

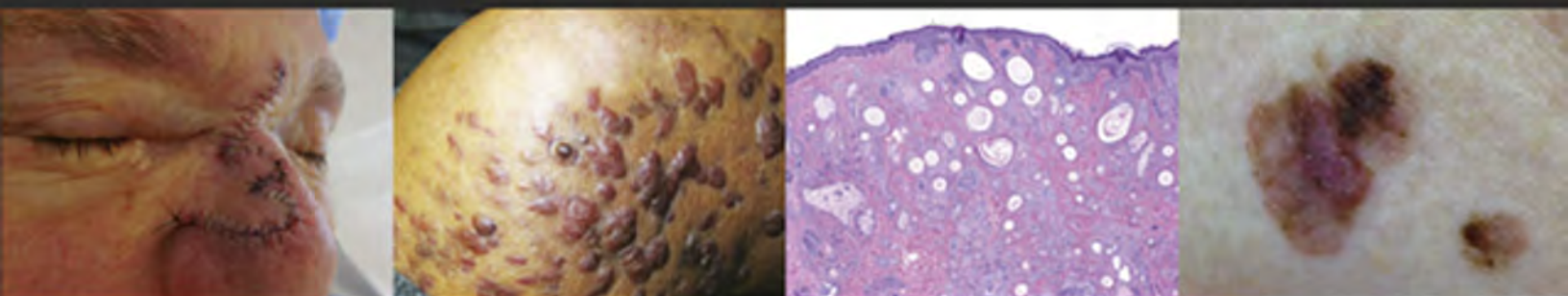
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# Review of **Dermatology**



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# Review of **Dermatology**

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# Preface

## Purpose of this book

We envision this book serving as a comprehensive review for dermatology residents and practicing dermatologists. We hope that the book is used not only in the United States, but all over the world.

## How the book should be used

The book can be used in many ways:

- As a resource for practicing dermatologists preparing for recertification examinations or simply as a quick reference
- As a resource for dermatology residents preparing for board examinations, in-service examinations, or simply as a quick reference (it could even be used throughout residency as a place to compile notes and facts learned from reading textbooks and journal articles, much the way First Aid® was used during medical school)

## How the book should NOT be used

There is NO substitution for reading textbooks and journal articles during residency. This book should serve as a review or a syllabus of dermatology, but should not take the place of textbooks and original literature. Many great resources to

truly learn dermatology exist – our favorites are *Dermatology* (commonly referred to as Bologna), *Andrews' Diseases of the Skin*, *Comprehensive Dermatologic Drug Therapy* (commonly referred to as Wolverton), *The Requisites in Dermatology Series* (particularly dermatopathology and dermatologic surgery), *Practical Dermatopathology* (commonly referred to as Rapini), and *Hurwitz Clinical Pediatric Dermatology*.

## Other information

Please remember that space was limited for this book, as it is for all books – we had to make important choices to leave certain information out of the book.

We are extremely grateful to the authors and editors of the textbooks listed above, as well as those of *McKee's Pathology of the Skin* and *Weedon's Skin Pathology*, as nearly all of the figures came from these resources.

Despite reading and re-reading this text many times, we imagine that some errors may have snuck by (particularly as this is our first edition). We encourage you to email us at [reviewofdermatology@gmail.com](mailto:reviewofdermatology@gmail.com) with any errors or suggestions so we can correct these for our second edition. Please also email us if you have ideas to improve the book or would like to contribute to future editions.



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- 3.8 Xanthomas
- 3.9 Urticaria and angioedema
- 3.10 Neutrophilic dermatoses
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- 3.22 Vasculitides, vasculopathies, and other vascular disorders
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# Dedications

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To my wife, for her unwavering and unconditional love and support

To my grandmother (Amma), who taught me the importance of sacrifice

To my parents, who always encouraged me to follow my dreams

To my sister, whose daily conversations keep me laughing

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# Basic Science

*Adnan Mir and Rahul Chavan*

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## 1.1 STRUCTURE AND FUNCTION OF THE SKIN

- Functions: interfaces with environment, collects sensory data, protects against infection and chemical penetration, temperature regulation, water retention, and excretion of drugs/waste
- Comprised of three layers: epidermis, dermis, and subcutis
  - Epidermis
    - Squamous epithelium comprised of keratinocytes connected by desmosomes, adherens junctions, tight junctions, and gap junctions (see [Table 1-1](#))
      - ◆ Intercellular junctions
        - **Desmosomes**: primary keratinocyte intercellular junction
          - ◇ Provide structure and integrity to the epidermis by anchoring/attaching to **keratins**
          - ◇ Consist of desmoplakin (cytoplasmic), plakophilin (cytoplasmic), plakoglobin (cytoplasmic), desmocollin 1/2/3 (transmembrane), and desmoglein 1/3 (transmembrane)
          - ◇ Desmocollin, desmoglein, and other cadherins are **calcium-dependent**
        - **Adherens junctions**: also mediate tight intercellular binding ([Fig. 1-1](#))
          - ◇ Anchor/attach to **actin** filaments
        - ◇ Consist of  $\alpha$ -catenin (cytoplasmic),  $\beta$ -catenin (cytoplasmic), plakoglobin (cytoplasmic), and classic cadherins (E and P; transmembrane)
      - **Tight junctions**: composed of claudins and occludins; form tight seal against water loss in granular layer
      - **Gap junctions**: facilitate intercellular communication; composed of **connexons** (tubular channels composed of **six connexins**)
    - Cells originate in the cuboidal basal layer and flatten out as they ascend to the surface – four to five layers/strata (deep to superficial): **stratum basale**, **s. spinosum**, **s. granulosum**, **s. lucidum** (only on palmoplantar surfaces), and **s. corneum**
    - **Stratum basale**: mitotically active cuboidal cells from which the upper layers of the epidermis are derived
      - ◆ Attached to dermis by hemidesmosomes
      - ◆ **Keratins 5 and 14 produced here**
      - ◆ Cellular proliferation stimulated by various factors, including trauma and UV ( $\uparrow$ **ornithine decarboxylase** expression is associated with (a/w) proliferative states)
        - Ornithine decarboxylase is inhibited by corticosteroids, retinoids, and vitamin D3
      - ◆ 10% of cells in the basal layer are stem cells, which give rise to other **stem cells** and **transient amplifying cells** that can still replicate, but only for a few cycles, until they reach a

Table 1-1. Intercellular Junction Proteins

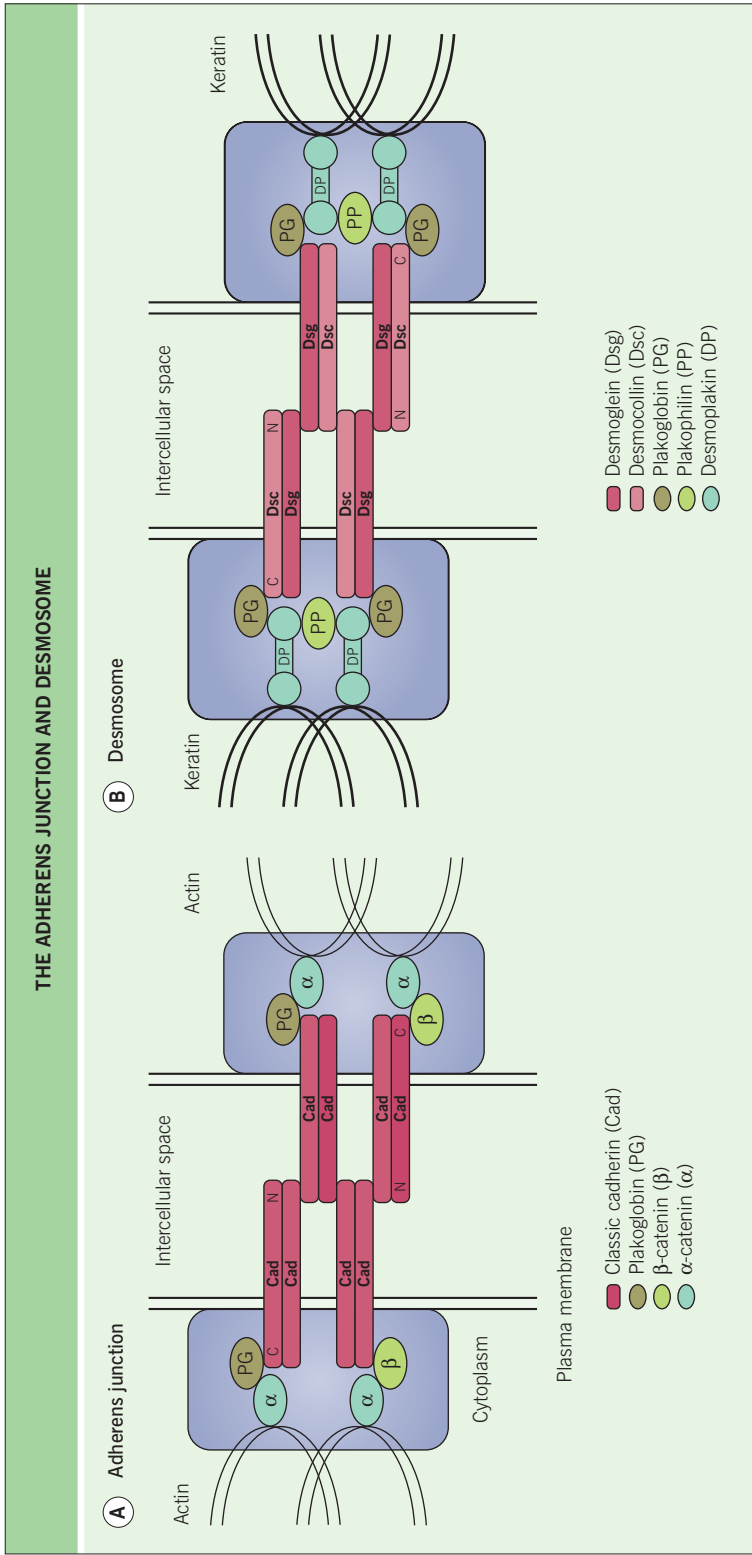
Protein	Protein Family	Junction Type	Disease State
Desmoglein 1	Cadherin	Desmosome	Autoimmune: pemphigus foliaceus, PNP, PV (mucocutaneous form), IgA pemphigus (intraepidermal neutrophilic type) Inherited: <b>striate PPK</b> Infectious: bullous impetigo and SSSS
Desmoglein 3	Cadherin	Desmosome	Pemphigus vulgaris (mucosal-predominant and mucocutaneous forms), PNP, IgA pemphigus (intraepidermal neutrophilic type)
Desmoglein 4	Cadherin	Desmosome	<b>Monilethrix</b> (autosomal recessive form), autosomal recessive hypotrichosis
Desmocollin 1	Cadherin	Desmosome	<b>IgA pemphigus (SPD type)</b>
Desmocollin 2	Cadherin	Desmosome	Carvajal-like phenotype in one family
Desmocollin 3	Cadherin	Desmosome	Hypotrichosis
Plakoglobin	Armadillo (catenin)	<b>Desmosome and Adherens</b>	<b>Naxos syndrome</b>
Plakophilin	Armadillo	Desmosome	Ectodermal dysplasia with skin fragility
Desmoplakin	Plakin	Desmosome	<b>Carvajal syndrome</b>
E-Cadherin	Cadherin	Adherens	Somatic mutations in many neoplasms
$\beta$ -Catenin	Armadillo	Adherens	Somatic mutations in many neoplasms, including <b>pilomatricomas</b> ; also may be seen in <b>myotonic dystrophy</b> and <b>Rubenstein-Taybi</b>
Connexin 26 (GJB2)	Connexin	Gap	<b>Vohwinkel syndrome</b> , <b>KID syndrome</b> , <b>Bart-Pumphrey syndrome</b> , <b>PPK with deafness</b> ; also common in nonsyndromic deafness!
Connexin 30 (GJB6)	Connexin	Gap	<b>Hidrotic ectodermal dysplasia</b>
Connexin 30.3 (GJB 4)	Connexin	Gap	<b>Erythrokeratoderma variabilis</b>
Connexin 31 (GJB 3)	Connexin	Gap	<b>Erythrokeratoderma variabilis</b>

terminal differentiation phase, where they move upwards and eventually desquamate

- ◆ Transit time from basal layer to stratum corneum = **14 days**; transit through the stratum corneum/desquamation = **14 days (total = 28 days)** from basal layer to desquamation)
- **Stratum spinosum**: named for the "spiny" appearance of intercellular desmosomal connections on microscopy
  - ◆ Contain multiple types of intercellular junctions
  - ◆ Keratins 1 and 10 made here
  - ◆ Terminal keratinocyte differentiation 2° to ↑intracellular calcium in suprabasal epidermis
  - ◆ Odland bodies (lamellar granules) are produced by Golgi bodies in spinous layer
    - ➔ Primarily contain **ceramide (most important lipid)** involved in epidermal barrier function; the most prevalent/important lipid in the stratum spinosum, along with glycoproteins, glycolipids, and phospholipids
    - ➔ Are specialized lysosomes that exert most of their action in the stratum corneum, by discharging ceramides and other lipids to the extracellular space of the junction between the stratum granulosum and stratum corneum ➔ **ceramides help form the cornified cell envelope** (see below), and eventually replace the cell membrane
    - ➔ Flegel's disease and Harlequin ichthyosis are 2° to ↓lamellar granules
    - ➔ **X-linked ichthyosis** occurs due to absent steroid sulfatase in lamellar granules
- **Stratum granulosum**: flattened cells with prominent basophilic **keratohyaline granules**,

which contain **profilaggrin** (converted to filaggrin at junction of stratum granulosum and stratum corneum), **loricrin**, keratin intermediate filaments, and involucrin

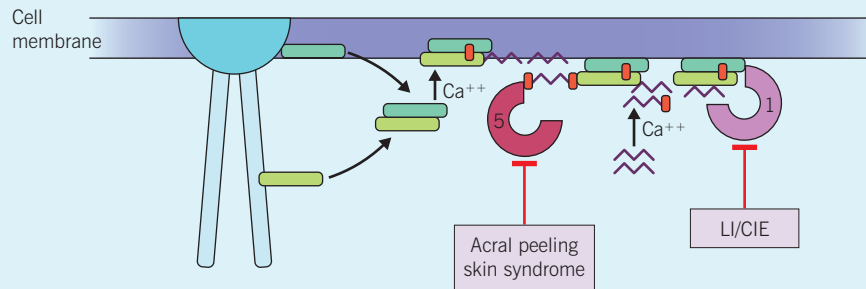
- ◆ Cells begin to lose nuclei, but keep overall structure
- ◆ **Cornified cell envelope** production primarily takes place in the granular layer (Fig. 1-2)
  - ➔ Cross-linked protein and lipid structure encased in extracellular lipids forming a strong polymer that eventually replaces the plasma membrane
    - ◇ Process starts with envoplakin, periplakin, and involucrin scaffolding along the inner cell membrane (which is eventually replaced by ceramides from lamellar granules)
    - ◇ Further reinforcement by cross-linking **loricrin (#1 component of cornified envelope, first appears in granular layer; mutated in Vohwinkel syndrome variant lacking deafness)**, small proline-rich proteins, keratin, and filaggrin
    - ◇ **Cross-linking occurs via transglutaminase I** ➔  $\gamma$ -glutamyl lysine isopeptide bonds (**Boards factoids**: TG-1 is mutated in lamellar ichthyosis; TG-3 is antigenic target in dermatitis herpetiformis)
    - ◇ Other components include envoplakin (helps connect desmosomes to cornified envelope), periplakin, elafin, and others
    - ◇ Outer surface of the cornified envelope is ultimately surrounded by lipids (primarily ceramide) = **cornified lipid envelope**



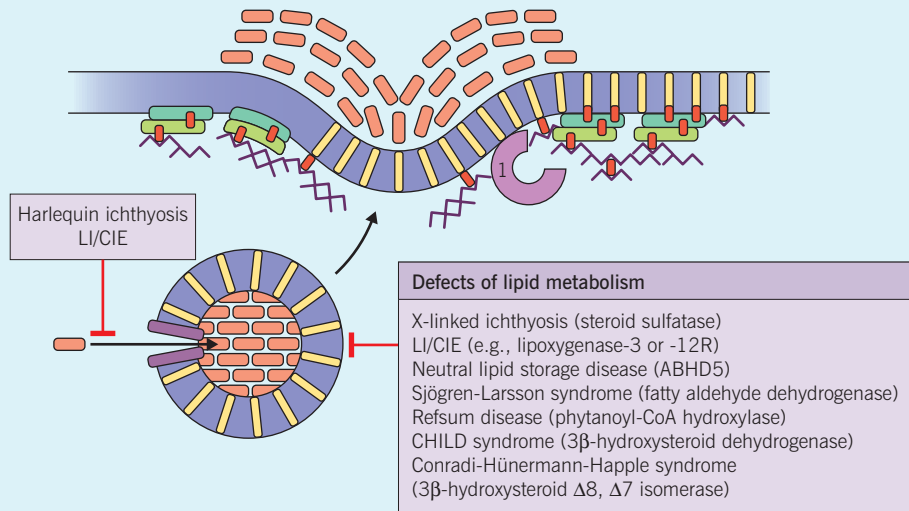
**Figure 1-1.** The adherens junction and desmosome. (A) The adherens junction complex contains classic cadherins as transmembrane constituents, and α-catenins, β-catenins, and plakoglobin as cytoplasmic constituents. A classic cadherin is directly coupled through its cytoplasmic tail to β-catenin or plakoglobin, which in turn is linked to α-catenin, which binds to actin. (B) The desmosome complex includes desmogleins and desmocollins as transmembrane constituents, and plakoglobin, plakophilin, and desmoplakin as cytoplasmic constituents. Desmogleins and desmocollins associate with plakoglobin, which in turn binds to desmoplakin and links keratin to the membrane. N = amino-terminus; C = carboxy-terminus. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

## FORMATION OF THE CORNIFIED CELL ENVELOPE (CE)

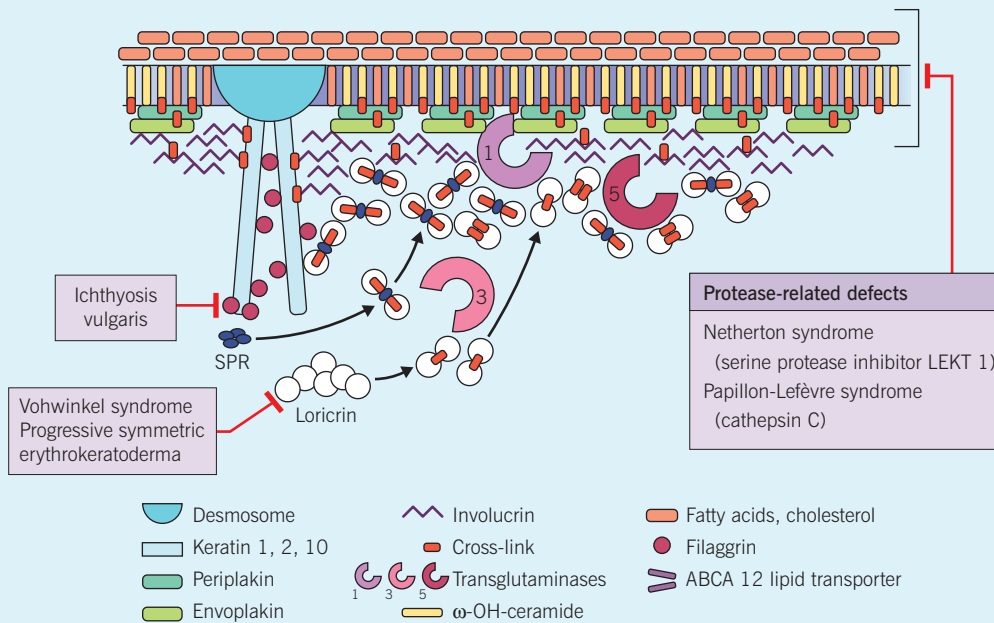
### 1 Initiation (spinous layer)



### 2 Lamellar granule extrusion (granular layer)



### 3 Reinforcement and lipid envelope formation (upper granular layer/interface with cornified layer)



**Figure 1-2.** Formation of the cornified cell envelope (CE). Terminal differentiation of keratinocytes is triggered by an increase in the intracellular  $\text{Ca}^{2+}$  concentration of the suprabasal epidermis. CE assembly is initiated in the upper spinous layer via formation of a cross-linked scaffold composed of envoplakin, periplakin, and involucrin along the inner surface of the cell membrane (1). This is followed by (or perhaps coincident with) extrusion of lamellar granules into the extracellular space (2). Specialized  $\omega$ -hydroxyceramides are delivered to, and eventually replace, the cell membrane, where they become linked to scaffold proteins. Reinforcement occurs via cross-linking and translocation to the cell periphery of loricrin (accounts for >80% of the mass of the CE) and small proline-rich proteins (SPRs) (3). Complexes of keratin and filaggrin also become cross-linked to the CE. In addition, proteases play important roles in processing of CE proteins and the proteolysis of corneodesmosomes that is required for desquamation. A mature and terminally differentiated cornified cell thus consists of keratin filaments covalently attached to the CE, which is composed of protein and lipid envelope components and is imbedded in the extracellular lipid lamellae. Defects in transglutaminases, lipid metabolism, CE structural proteins, and proteases leads to a variety of diseases characterized by ichthyosis and/or keratoderma (1–3). CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; LI, lamellar ichthyosis; CIE, congenital ichthyosiform erythroderma. (Courtesy, Julie V Schaffer, MD) (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

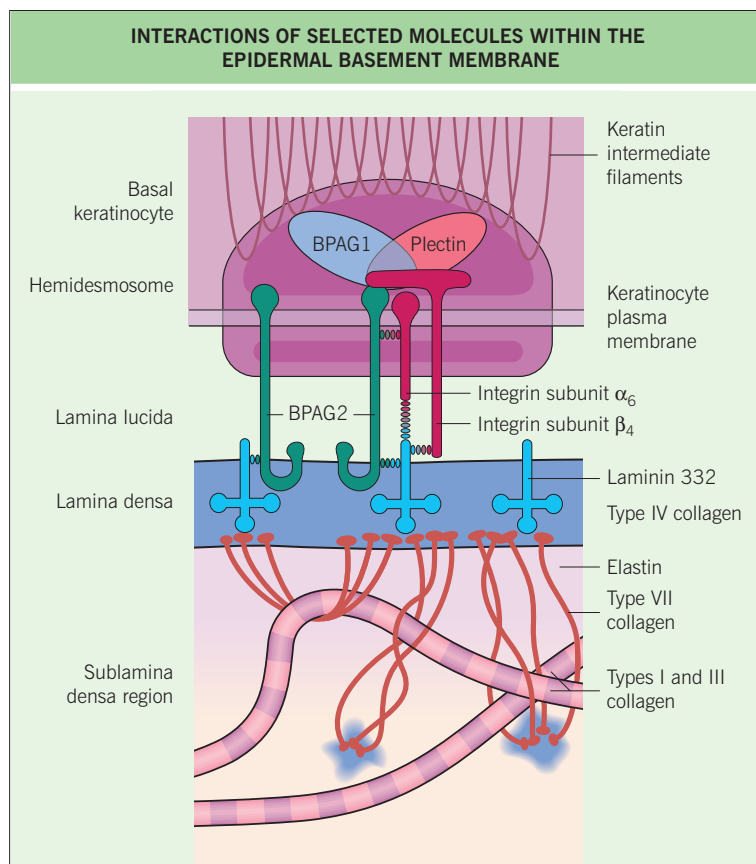
- ◊ Ultimately provides strong water-impermeable outer barrier
- **Stratum corneum:** outermost layer, which serves as a mechanical barrier between the epidermis and the environment
  - ◆ Composed primarily of protein-rich corneocytes ("bricks"; **contain NO nuclei**; keratin filaments attached to cornified envelope) embedded in a lipid matrix ("mortar," cornified lipid envelope)
  - ◆ Serves as a barrier to water loss (conditions that perturb the skin → ↑ transepidermal water loss) and toxins/infectious agents
- Epidermal cells of importance
  - ◆ **Keratinocytes** are the primary cells of the epidermis and produce proteins (e.g., keratin filaments) and lipids important for barrier function
    - Keratins: intermediate filaments that comprise the primary cytoskeleton of the epidermis (see Table 1-3)
      - ◊ Type I keratins: **low-MW; acidic; K9-28, K31-40** (hair keratins); **chromosome 17**
      - ◊ Type II keratins: **high-MW; basic; K1-8, K81-86** (hair keratins); **chromosome 12**
      - ◊ Basic structure is an  $\alpha$ -helical rod domain (consisting of heptad amino acid repeats) divided into four segments (1A, 1B, 2A, and 2B) that are interrupted by three nonhelical segments ("linkers")
      - ◊ Functional unit consists of **heterodimers of type I and type II** filaments that form tetramers and ultimately filaments
      - ◊ Anchored to plasma membrane by desmosomes
      - ◊ 40–70 kD
    - Keratinocytes produce IL-1, IL-6, IL-8, IL-10, IL-12, and TNF- $\alpha$ , among others
    - Keratinocytes respond to IL-2, IL-4, IL-13, IL-22, and TNF- $\alpha$ , among others
  - ◆ **Melanocytes**
    - **Neural crest-derived** melanin-producing dendritic cells found in the stratum basale ( $\approx 1:10$  ratio with keratinocytes, when viewed in 2-dimensional plane)
      - ◊ **c-kit** activation is needed for melanocyte development/migration; **piebaldism** occurs as a result of c-kit loss → impaired melanocyte migration and proliferation; **c-kit mutations** are a/w mucosal and acral melanoma
    - Each melanocyte interfaces with **36 keratinocytes** when analyzed three-dimensionally (**epidermal melanin unit**)
    - Melanin is produced in melanosomes (lysosome-type organelles) from its precursor, tyrosine, through a multistep enzymatic process involving **tyrosinase (copper-dependent enzyme)**
      - ◊ Tyrosine → (tyrosinase-dependent step) DOPA → (tyrosinase-dependent step) DOPAquinone → **pheomelanin** (yellow/red; made by round melanosomes) or **eumelanin** (black/brown; made by elliptical melanosomes)
- ◊ Melanosomes are transported along dendritic processes and transferred to keratinocytes through phagocytosis of dendrite tips
- ◊ Racial variation in pigmentation: identical melanocyte density in dark and light skinned individuals; **melanosomes in darker skinned individuals are larger, darker (↑ melanin), more stable, and are transferred individually** (vs smaller, lighter, less stable, and **clustered** melanosomes in lighter skin)
- ◊ Melanin production is stimulated by melanocyte-stimulating hormone (**MSH**) and **ACTH** activity on **MC1-R** on melanocytes; also stimulated through various pathways induced by UV radiation
- ◊ **MC1-R loss of function mutations** → **↑ pheomelanin:eumelanin ratio** (phenotype = **red hair/fair skin, ↑ risk of melanoma**)
- ◊ Melanin absorbs UV → protects against UV-induced mutations
- ◊ UV exposure → **immediate tanning** (from oxidation of existing melanin) and **delayed tanning** (requires new melanin synthesis)
- Other high-yield examination facts:
  - ◊ Defects in enzymes required to convert tyrosine to melanin → **oculocutaneous albinism**; OCA1 (*Tyrosinase*), OCA2 (*P gene*), OCA3 (*TRP-1*)
  - ◊ Defects in packaging of melanosome-specific proteins → **Hermansky-Pudlak syndrome** (HPS1 > HPS3 > other gene mutations)
  - ◊ Defects in lysosome and melanosome trafficking to dendrites → **Griscelli** (*MYO5A*, *RAB27A*, and *MLPH* mutations) and **Chédiak-Higashi syndrome** (*LYST* mutations)
- ◆ **Langerhans cells (LCs):** major antigen presenting cells (APC) of the skin
  - Dendritic histiocytes characterized by **reniform** (kidney shaped) nuclei, and tennis racket-shaped **Birbeck granules** seen on electron microscopy
  - Interact with keratinocytes via E-cadherin
  - Positive immunostains: **CD207 (langerin;** most sensitive IHC stain; specific for Birbeck granules), **CD1a, S100, CD34, vimentin, and actin**
  - Originate from CD34+ progenitor cells in bone marrow like other monocytes/macrophages
  - Found mainly in stratum spinosum, where it first encounters and processes antigens, and **subsequently migrates to the lymph nodes** to activate T-cells
  - **Downregulated in skin after UV exposure** → ↓ immune surveillance
  - See p. 24 for further discussion of function



- ◆ **Merkel cells:** slow-adapting mechanoreceptors found in fingertips, lips, oral cavity, and hair follicle ORS
  - Found in stratum basale; communicate with neurons
  - **CK20<sup>+</sup> in perinuclear dot pattern** sensitive/specific for Merkel cells; also (+) for neurofilaments, S100, synaptophysin, chromogranin A, vasoactive intestinal peptide, neuron-specific enolase, and calcitonin gene-related peptide
- **Basement membrane zone (BMZ)** (Fig. 1-3 and see Table 1-2)
  - Semipermeable barrier between epidermis and dermis that also serves to adhere basal keratinocytes to the underlying dermis
  - Key steps within each location:
    - ◆ **Basal keratinocyte/hemidesmosome:** intracellular keratin filaments (K5 and K14) attach to electron-dense hemidesmosomal plaques (**plectin** and **BPAG1 [BP230]**) on the basal plasma membrane → hemidesmosomal plaque proteins bind to intracellular portions of the anchoring filaments (BPAG2 and  $\alpha_6\beta_4$  integrin)
    - ◆ **Lamina lucida:** extracellular portion of **anchoring filaments** (BPAG2,  $\alpha_6\beta_4$  integrin, and **laminin 332**) extend from the hemidesmosome down to the lamina densa;

the thin filaments result in an electron-lucent region; is the weakest portion of BMZ → is zone of separation in **salt-split skin** and also in **suction blisters**

- ◆ **Lamina densa:** anchoring filaments attach to **type IV collagen** (#1 component) and other proteins (laminin 332, laminin 331, and nidogen) in the lamina densa → results in attachment between basal keratinocyte and lamina densa
- ◆ **Sublamina densa:** loops of **type VII collagen (anchoring fibrils)** arise from the underside of lamina densa, extend down into the dermis, hooking around dermal **type I and III collagen fibers**, and then loop back up to reattach to lamina densa (or anchoring plaques in dermis) → firmly anchors the lamina densa (and all aforementioned structures) to the papillary dermis
- BMZ also functions as a permeability barrier: **heparan sulfate** proteoglycan (**negatively charged**) in lamina densa is a major contributor
- **Dermis**
  - Located below the epidermis, derived from mesoderm, and divided into papillary dermis (superficial) and reticular dermis (deep)
  - Cells of significance
    - ◆ **Fibroblasts**-create extracellular matrix and are involved in wound healing



**Figure 1-3.** Interactions of selected molecules within the epidermal basement membrane. These interactions promote epidermal adhesion and also play a key role in a number of dermatologic diseases. Important molecular interactions include those between: (1) plakin family members, BPAG1 and plectin, with keratin intermediate filaments; (2) the former with BPAG2 and integrin  $\alpha_6\beta_4$  (specifically the large cytoplasmic domain of integrin subunit  $\beta_4$ ); (3) the cytoplasmic domains of BPAG2 and integrin subunit  $\beta_4$ ; (4) the extracellular domains of BPAG2 and integrin subunit  $\alpha_6$  as well as laminin 332 (formerly laminin 5); (5) integrin  $\alpha_6\beta_4$  in hemidesmosomes and laminin 332 in the lamina densa; (6) laminin 332 and type VII collagen; (7) type VII collagen with type IV collagen, fibronectin, and type I collagen in the sublamina densa region. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 1-2.** Basement Membrane Zone Proteins

Protein	Site	Source	Family	Function	Disease State
BPAg1 (230 kD)	Hemidesmosome/keratinocyte	Keratinocyte	Plakin	Binds keratins and integrins; intracellular/part of attachment plaque	BP, EB simplex
BPAg2 (180 kD)	Hemidesmosome/keratinocyte → lamina lucida Amino terminus is intracellular and carboxy terminus is extracellular -NC16A domain is closer to amino terminus but is extracellular	Keratinocyte	Collagen (XVII)	Transmembrane protein and one of the anchoring filaments; interacts with BPAg1, laminin 5, $\beta$ 4 integrin, and plectin	N16A Terminus: BP, pemphigoid gestationis, linear IgA bullous disease Carboxy Terminus: Cicatricial pemphigoid
$\alpha\beta$ 4 Integrin	Hemidesmosome/keratinocyte → lamina lucida	Keratinocyte	Integrin	Interacts with keratins, laminin 5, plectin, BPAg1, BPAg2; part of the anchoring filaments	<b>Ocular</b> cicatricial pemphigoid (antibodies to <b><math>\beta</math>4</b> ), <b>EB with pyloric atresia</b> (85%)
Laminin 332 (laminin 5, epiligrin)	Lamina lucida → Lamina densa	Keratinocyte	Laminin	Connects other anchoring filaments (BPAg2 and $\alpha\beta$ 4 integrin) to collagen VII; part of the anchoring filaments	<b>Antiepiligrin pemphigoid</b> (a/w malignancy), <b>JEB-Herlitz</b>
Plectin	Hemidesmosome	Keratinocyte	Plakin	Binds keratins and integrins; intracellular/part of attachment plaque	<b>EB with muscular dystrophy</b> , EB with pyloric atresia (15%)
Nidogen (entactin)	Lamina densa	Unclear	Nidogen	Adaptor between laminin 1 and collagen IV in lamina densa; stabilizes proteins of lamina densa	
Collagen IV	Lamina densa	Unclear	Collagen	Anchors laminins in lamina densa → structural support; also a component of <b>anchoring plaques</b> in dermis, which attach collagen VII to collagen I and III	Goodpasture disease, Alport syndrome
Collagen VII	Sublamina densa	Fibroblasts	Collagen	Major component of anchoring fibrils	<b>Dystrophic EB, bullous lupus, EB acquisita</b>
Heparan sulfate proteoglycan	Lamina densa	Fibroblasts	Proteoglycans	Contribute to matrix of and give an overall <b>negative charge (creating a permeability barrier)</b> to the basement membrane	

- ◆ Mononuclear phagocytes – discussed on p. 23
- ◆ Mast cells – discussed on p. 23
- ◆ Glomus cells – specialized smooth muscle cells derived from **Sucquet-Hoyer canals**, which allow for blood **shunting** from arterioles to venules (bypassing capillaries); found mainly in the **palms/soles**
  - ➔ Overproduction ➔ glomus tumor (favors acral sites because of ↑glomus cell density)
- ◆ Dermal dendritic cells – bone marrow-derived APC that resides within dermis; **highly phagocytic**
- Extracellular matrix (ECM)
  - ◆ Provides structure and support to the dermis; essential for water retention and for signal transduction
  - ◆ Synthesized by dermal fibroblasts
  - ◆ Composed of collagens, elastin, fibrillins, fibulins, integrins, laminins, glycoproteins, and proteoglycans
    - ➔ Collagens are **triple helices** formed by amino acid chains where every third residue is **glycine (Gly-X-Y)**, with a high likelihood of **proline** and **hydroxyproline/hydroxylysine** in the X and Y positions, respectively
- ◆ Accounts for 75% of dry weight of the skin; #1 component of the dermis
- ◆ **Collagen I is the primary collagen** (85%) of the ECM; type III (10%; important and prevalent in **blood vessels**, fetal skin, GI tract, new scars, and keloids) and V are also present
- ◆ **Lysyl hydroxylase** and **proline hydroxylase** catalyze crosslinking of collagen; **vitamin C-dependent process** (deficiency ➔ scurvy)
- ◆ Defects in collagen and/or collagen cross-linking result in most forms of Ehlers-Danlos syndrome: **COL1A1/2** (EDS arthrochalasia type, and osteogenesis imperfecta); **COL3A1** (EDS vascular type); **COL5A1/2** (classical EDS); **Lysyl hydroxylase/PLOD1** gene (EDS kyphoscoliosis type)
- ◆ Matrix metalloproteinases degrade collagen
- ◆ Retinoids ➔ ↑collagen production
- ◆ Corticosteroids and UV ➔ ↓collagen production
- ➔ Elastic fibers provide resilience from stretching and modulate TGF- $\beta$  and BMP signaling

**Table 1-3.** Protein Components of the Epidermis (Including Nonepidermal Keratins)

Protein	Site of Synthesis	Function	Disease State
Keratin 1	Suprabasal keratinocytes (produced in spinous layer)	Primary keratinocyte cytoskeleton	Epidermolytic ichthyosis (preferred new name for EHK), epidermolytic and nonepidermolytic (Unna-Thost) PPK, ichthyosis hystrix of Curth-Macklin*
Keratin 2	Granular layer		Superficial epidermolytic ichthyosis (Siemens)
Keratin 3	Cornea		Meesmann's corneal dystrophy
Keratin 4	Mucosal epithelium		White sponge nevus
Keratin 5	Basal keratinocytes		EBS, Dowling-Degos disease*
Keratin 6a	Outer root sheath of hair		Pachyonychia congenita I*
Keratin 6b	Nail bed epithelium		Pachyonychia congenita II
Keratin 9	Palmoplantar suprabasal keratinocytes		Vorner (epidermolytic) PPK
Keratin 10	Suprabasal keratinocytes (produced in spinous layer)		Epidermolytic ichthyosis*
Keratin 11	Granular layer		
Keratin 12	Cornea		Meesmann's corneal dystrophy
Keratin 13	Mucosal epithelium		White sponge nevus
Keratin 14	Basal keratinocytes		EBS, Naegeli-Franceschetti-Jadassohn syndrome, dermatopathia pigmentosa reticularis
Keratin 16	Outer root sheath of hair		Pachyonychia congenita I*
Keratin 17	Nail bed epithelium		Pachyonychia congenita II, steatocystoma multiplex
Keratin 19	Stem cells of basal layer		
Keratin 71, 73, 74	Hair inner root sheath		Wooly hair
Keratin 32, 35, 82, 85	Hair cuticle		
Keratin 17, 33, 34, 36, 37, 75, 81	Hair medulla		Pseudofolliculitis barbae
Keratins 31–38, 81, 83, 85, 86	Hair cortex		Monilethrix ( <i>KRT81</i> , <i>KRT83</i> , <i>KRT86</i> most commonly; also <i>DSG4</i> )
Filaggrin/profilaggrin	Granular layer	Aggregates keratin, flattening granular layer cells. Degraded in the stratum corneum into <b>urocanic acid</b> and pyrrolidone carboxylic acid, which <b>help block/absorb UV radiation</b> . Urocanic acid is also a component of <b>natural moisturization factor</b> – helps keep stratum corneum hydrated/moist	Ichthyosis vulgaris, atopic dermatitis
Loricrin	Granular layer	<b>Most abundant component of cornified cell envelope.</b> Cross-linked to involucrin by transglutaminase 1**.	Vohwinkel syndrome with ichthyosis (NO deafness) Decreased in psoriasis
Involucrin	Granular layer	Component of cornified cell envelope. Proteins are cross-linked together by transglutaminase 1 → strong border	Increased in psoriasis

\*In psoriasis and other hyperproliferative states, keratin 6 and 16 are upregulated and keratin 1 and 10 are downregulated

\*\*Transglutaminase 1 mutations → lamellar ichthyosis and NBCIE

- ◇ Account for 4% of dry skin weight
- ◇ **90% elastin** (core) and **10% fibrillin** (surrounds elastin); elastin contains high levels of **desmosine** and **isodesmosine** → these crosslink with fibrillin via **lysyl oxidase** (copper necessary for function)
- ◇ Notable defects in elastic tissue: **Fibrillin 1** mutation (Marfan's syndrome); **Fibrillin 2** mutation (Congenital contractural arachnodactyly); **Fibulin 5** (Cutis laxa; gene defect results in decreased desmosine); **LEMD3** mutation

(Buschke-Ollendorf syndrome; defect results in increased desmosine); **ABCC6** mutation (Pseudoxanthoma elasticum; mutation results in fragmentation and calcification of elastic fibers)

- ◇ **Elaunin** fibers run horizontal/parallel in reticular dermis and **oxytalan** fibers run vertical/perpendicular to DEJ in papillary dermis; **mnemonic: "stand"** (= vertical) **up-high** (= high in dermis) with **OXYgen** (= **OXYtalan**)
- ◇ UV radiation → damage of elastic fibers

- ◆ All aforementioned fibers are set in a matrix of proteoglycans and glycosaminoglycans (GAGs) that **retain large quantities of water** (up to 1000× their volume!) = ground substance
  - Most important GAGs = **hyaluronic acid**, chondroitin sulfate, dermatan sulfate, and heparan sulfate
  - GAGs are broken down by lysosomal hydrolases
- Cutaneous vasculature
  - ◆ Cutaneous vasculature important for metabolic support of the skin and maintenance of body temperature
  - ◆ Two vascular plexuses: superficial (→ vessels of the reticular dermis) and deep (→ follicles, glands)
  - ◆ VEGF is the primary mediator of **vasculogenesis**
    - ↑VEGF: most cancers, psoriasis, POEMS syndrome, and other diseases with increased vasculature
  - ◆ Lymphatic vessels collect fluid and proteins from interstitium and direct it into the lymph circulation
  - ◆ **Prox1, Podoplanin (D2-40), LYVE-1**, and VEGFR-3 are lymphatic vessel markers
- Cutaneous neurology
  - ◆ Nerves of the skin are responsible for detecting touch/pressure, pain, itch, and other sensations
  - ◆ Cutaneous sensory nerves are divided into free nerve endings and corpuscular nerve endings (round/globular collection of neural and other cells)
    - Free nerve endings
      - ◇ **Itch and pain**: A-δ (larger; myelinated) and C-polymodal nociceptor afferent fibers (smaller; unmyelinated)
      - ◇ End in the epidermis/superficial dermis
    - Specialized nerve receptors (corpuscular nerve endings)
      - ◇ Krause end bulbs: **genitalia**, perianal region, and vermillion lips; mnemonic “Krazy **Krause ends** on erotic areas”
      - ◇ Meissner’s corpuscle: superficial (dermal papillae) mechanoreceptor of **digits**; fast adapting; suited for pressure/light touch
      - ◇ Pacinian corpuscle: deep (deep dermis/fat) mechanoreceptor of palmoplantar skin, nipples, and genital region; fast adapting; suited for **vibration** and deeper pressure
      - ◇ Merkel nerve ending: superficial (basal epidermis) mechanoreceptor most concentrated in fingertips, lips, and external genitalia; slow adapting; suited for pressure/touch
      - ◇ Ruffini corpuscle: deep (fat) mechanoreceptor most concentrated around fingernails; slow adapting; suited for **sustained pressure**
- ◆ Innervation of cutaneous appendages:
  - Adrenergic control: **vascular smooth muscle**, **apocrine** glands, and arrector pili contraction
  - Cholinergic control: **eccrine** glands
- Adnexal structures
  - Eccrine glands
    - ◆ Secretory exocrine gland primarily responsible for **thermoregulation** and waste excretion
    - ◆ Found on all cutaneous surfaces except: external auditory canal, lips, glans penis, clitoris, and labia minora
    - ◆ Highest concentration = palms and soles
    - ◆ Controlled by hypothalamus; innervated by **postganglionic sympathetic fibers**, which synapse with **muscarinic acetylcholine receptors** on the glands
    - ◆ Isotonic sweat secreted in secretory gland → NaCl reabsorbed in duct → **hypotonic sweat** is delivered to surface
      - ↑rate of sweating → more isotonic solution (less time to reabsorb in duct)
      - Maximal rate of sweating ~ 3 L/hr
      - Merocrine secretion
    - ◆ Components (deep to superficial): secretory coil (deep dermis), intradermal/straight duct (eosinophilic cuticle seen on histology), and acrosyringium (intraepidermal portion; spiral duct that opens onto the skin surface)
    - ◆ Stains for S100, keratin, and CEA
  - Apocrine glands
    - ◆ Secretory exocrine glands with unclear function in humans, though in animals they mediate sexual attraction through pheromone release
      - Activity begins around puberty
    - ◆ Located primarily in **anogenital skin**, **axillae**, external ear canal, vermillion border, **periumbilical region**, eyelid margin, and breast
    - ◆ Empty into follicular infundibulum (above sebaceous duct)
    - ◆ Secretory control unclear → glands noninnervated, but do have **β-adrenergic receptors**, which are likely **stimulated by circulating catecholamines**
    - ◆ Secretory products released through **decapitation secretion**: cholesterol and cholesterol esters, triglycerides, squalene, and fatty acids
      - **Lipofuscin** = pigmented mixture of lipids and proteins → responsible for yellow-brown color of **chromhidrosis**
    - ◆ Initially odorless secretions → later modified by surface bacteria → results in body odor
    - ◆ Ectopic or modified apocrine glands: **mammary glands**, ceruminous glands of the external auditory canal, and **Moll’s gland of the eyelids**
      - These empty directly to the surface
  - Sebaceous glands
    - ◆ Secretory exocrine glands found primarily on the scalp, face, and upper anterior trunk (“seborrhic areas”)
      - NOT on the palms/soles

- ◆ Functions include water retention and innate immune defense
- ◆ Consist of sebocytes, which contain lipid vacuoles
- ◆ **Normally associated with hair follicles** and empty into inferior portion of the infundibulum
- ◆ Pubertal androgen production is major signal for sebaceous gland maturation (under adrenergic control)
  - ➔ Transient maternal androgen stimulation present in infancy
- ◆ Other endocrine factors stimulating maturation and sebum production: MSH, CRH, and substance P
- ◆ Secretory products released through **holocrine secretion** (entire cell lyses to release contents):
  - ➔ **Triglycerides (#1 component; ≈50%)** > wax esters (#2) > squalene (#3)
  - ➔ Others: cholesterol esters, cholesterol, antimicrobial peptides, androgens, and cytokines
- ◆ **Ectopic sebaceous glands:** Meibomian glands on eyelid tarsal plate, Fordyce spots (vermillion lip/oral mucosa), Montgomery tubercles (areolae/nipples), Tysons glands (labia minora/prepuce), and Zeis glands (eyelid margin, close to Moll's gland)
- Hair
  - ◆ Epithelial-derived appendage important for temperature regulation, protection of other

- structures (nasal mucosa, eyes, and ears), social and sexual cues, and tactile sensory input
- ◆ Three types of hairs:
  - ➔ Lanugo – fine hairs shed late in gestation and during the first month of life
  - ➔ Vellus – fine hairs over face, trunk, and extremities early in life
  - ➔ Terminal – coarse, darker hairs of scalp, eyebrows, and eyelashes; postpubertal androgens induce switch to terminal hairs in other sites
- ◆ Hair density: ~100,000 hairs on scalp; more in blonde and fewer in red-haired individuals
- ◆ Anatomy: [Table 1-4](#)
- ◆ Follicular layers (outer to inner): glassy membrane, outer root sheath, inner root sheath (Henle's layer, Huxley's layer, and cuticle), and hair shaft (cuticle, cortex [where most hair keratins located], and medulla)
  - ➔ Cuticle helps keeps hair intact – damage ➔ split ends (trichoptilosis)
  - ➔ Cuticle from hair shaft and inner root sheath merge
- ◆ Dermal papilla: mesenchymal structure (from embryonic mesoderm) containing vasculature; contributes to hair cycle regulation
- ◆ Hair cycle: [Table 1-5](#)
  - ➔ Exogen: phase of active shedding of club hair between telogen and anagen
    - ◇ Lose about 100 hairs/day

**Table 1-4.** Hair Anatomy

Portion of Hair	Description
Hair bulb	Lowermost portion of the hair follicle
Hair matrix	Rapidly proliferating keratinocytes that terminally differentiate to produce the hair shaft
Infundibulum	Region extending from the skin surface down to the point where the sebaceous gland opens into the hair follicle; ORS displays cornification similar to that of the interfollicular epidermis (i.e., contains <b>keratohyaline granules</b> )
Isthmus	Region located between the opening of the sebaceous gland, down to the site of insertion of the arrector pili muscle; ORS displays <b>trichilemmal keratinization</b> (no inner root sheath and IRS is shed before this point)
Lower hair follicle	Region located between hair bulb to proximal isthmus; encapsulates dermal papilla; has inner and outer root sheaths; <b>critical line of Auber</b> is the widest area
Arrector pili muscle	Inserts at the level of the bulge; pulls up hair ("goose bumps")
Bulge	Segment of the outer root sheath located at the level of arrector pili muscle insertion; major seat of epithelial <b>stem cells of the hair follicle</b>
Secondary hair germ	Additional seat of epithelial and also of melanocyte stem cells; located between club hair and dermal papilla in telogen hair follicle
Connective tissue sheath (CTS)	Special mesenchymal follicular sheath that is tightly attached to the hair follicle basement membrane and is continuous with the follicular dermal papilla
Follicular dermal papilla (DP)	Onion-shaped, closely packed, specialized fibroblast population with inductive and morphogenic properties; hair cycle-dependent fibroblast trafficking occurs between CTS and DP; volume of DP determines size of hair bulb and, thus, hair shaft diameter
Inner root sheath (IRS)	Packages and guides the hair shaft; cornifies normally; stains red secondary to citrulline; <b>not present in telogen hairs</b> ; is present in lower hair follicle but not in the isthmus/infundibulum
Outer root sheath (ORS)	Merges distally into the epidermis and proximally into the hair bulb; provides slippage plane, nutrition, regulatory molecules, and stem cells
Critical line of Auber	Widest section of the hair bulb and where most mitotic activity essential for hair growth occurs
Follicle pigmentary unit	Melanin-producing hair follicle melanocytes located up and around the upper one-third of the DP; transfer pheomelanosomes or eumelanosomes to differentiating hair follicle keratinocytes in the precortical matrix; goes largely into apoptosis during each catagen phase, regenerated from melanocyte stem cells in hair germ during anagen

(Adapted from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Table 1-5.** Hair Growth Cycle

	Anagen	Catagen	Telogen (Club Hairs)
Phase activity	Growth (~0.4 mm/day or ~1 cm/month on scalp); follicular melanocytes only active in anagen phase)	Regression ( <b>melanocytes in matrix apoptose</b> ; inner root sheath lost)	Resting
Duration	2–6 years	2–3 weeks	3 months
Percentage (%) of scalp hairs	85–90	1–2	10–15

→ Kenogen: subphase of telogen in which no shaft is present

- ◆ Color of hair 2° to hair melanocytes in **anagen bulb/matrix** (**melanin unit = 1 melanocyte: five keratinocytes**; melanocytes only produce pigment in anagen phase!)

→ Eumelanin (brown/black hair pigment) vs pheomelanin (red/blonde hair pigment)

- ◆ **Hair follicle stem cells** reside in **bulge** and contribute to hair cycling, **tissue regeneration**, and wound healing; follicular melanocytes can migrate to interfollicular areas in disease states (e.g., vitiligo) to assist with repigmentation

→ As with interfollicular stem cells in the basal layer of skin (see p. 1), also produce transient amplifying cells with restricted mitotic capacity

- ◆ **Disulfide bonding** via cysteine residues determines **curliness of hair** – these bonds are broken when hair is straightened, but subsequently reform with time

#### ○ Nail

- ◆ Appendageal structure important for protection and function of fingertips, for proper function of the feet, ability to scratch, and aesthetic appearance
- ◆ Plate is composed of keratin-producing onychocytes
- ◆ Important anatomic structures: [Table 1-6](#)
- ◆ Growth rate
  - Fingernails: 2 to 3 mm/month (~6 months to grow out)
  - Toenails: 1 mm/month (~12 months to grow out)

## 1.2 EMBRYOLOGY

- Skin structures derived from two of three primary germ layers
  - Ectoderm: epidermis, adnexal structures, Merkel cells, melanocytes (neural crest), and nerves (neuroectoderm)
  - Mesoderm: fibroblasts, LCs, vessels, and inflammatory cells
- Epidermis
  - 5 weeks: outer periderm and inner basal epidermal layer

**Table 1-6.** Nail Anatomy

Nail Location	Description
Proximal nail fold	Superficial layer continuous with skin, deep layer continuous with nail matrix
Eponychium (cuticle)	Located between nail plate and nail matrix; acts as seal against the environment
Nail matrix	At the proximal end of nail unit, generates the plate. <b>Proximal matrix → superficial portion of nail plate; distal matrix → ventral portion of plate.</b> Melanocytes found in nail matrix
Lunula (distal nail matrix)	Junction between matrix and bed
Nail plate	Hard, functional unit of nail, composed primarily of keratins; strong attachment to nail bed
Nail bed	Extends from lunula to onychodermal band. Provides support for nail plate. <b>Very minimal contribution to nail plate synthesis</b>
Onychodermal band	Red/pink transverse band marking end of bed
Hyponychium	Continuous with ventral edge of free nail plate and distal fingertip skin
Lateral nail folds	Guide growth of nail plate

- 8 weeks: epidermal stratification
- 9–12 weeks: **melanocytes**, LCs, and **Merkel cells** migrate into the epidermis
- Late second trimester: terminal differentiation, with **full stratification**
- Basement membrane, dermis, and subcutis
  - 6–8 weeks: fibroblasts appear beneath the epidermis
  - 9 weeks: distinct border between epidermis and dermis (DEJ present)
  - 9–12 weeks: primordial vasculature formed
  - 16–18 weeks: initial fat formation in subcutis
  - 20 weeks: mature thickness of dermis and dermal ridges present
- Hair
  - 9–12 weeks: **initial follicle development** on the **eyebrows, scalp, upper lip, and chin** – spreads **caudally and ventrally**; epidermal placodes (derived from ectoderm) induce underlying dermal papilla formation (derived from mesoderm)
  - 18–20 weeks: hair canal fully formed
  - 24–28 weeks: initiation of cycling through anagen, catagen, and telogen
    - Sonic hedgehog is an important molecule for telogen to anagen transition
- Nails
  - 8–10 weeks: nail bed demarcation
  - 12 weeks: proximal nail folds formed
  - 17 weeks: nail plate formed, covers nail bed by week 20
- Adnexal glands
  - 10 weeks: eccrine gland anlage formation on palms and soles
  - 14–16 weeks: eccrine primordia bud down, glands begin to develop

- 22 weeks: initiation of truncal eccrine gland formation; eccrine glands and ducts nearly mature on volar skin
- Apocrine gland formation initiated later than eccrine glands, at 22 weeks
- Sebaceous gland formation parallels hair follicle development (derived from outer root sheath)
- Melanocytes
  - Neural crest-derived cells, migrate under the direction of **KIT** and **KIT ligand**
  - 12 weeks: melanocytes present in epidermis
  - 12–16 weeks: melanin production begins
  - 16–20 weeks: melanocytes proliferate and become fully functional (transfer melanosomes to keratinocytes)
- Skin stem cell biology
  - Epidermal stem cells responsible for maintenance, repair, and renewal of epidermis
  - Keratinocyte stem cells located within the **bulge region** of the hair follicle and at the **base of rete ridges** of interfollicular epidermis
  - Complete renewal of epidermis every 40 to 56 weeks
  - Stem cells are multipotent with unlimited capacity to divide
  - Asymmetric division gives rise to transient amplifying cells, which divide rapidly to produce terminally differentiated cells

### 1.3 WOUND HEALING

- Three phases: inflammatory, proliferative, and remodeling
  - **Inflammatory phase** (starts within first 6–8 hours, and can last 3–4 days):
    - Clot formation and coagulation are initial steps
      - ◆ **Platelets come to site of wound first** → release various factors (ADP, clotting factors, PDGF, EGF, fibrinogen, fibronectin, TGF $\alpha$ , and TGF $\beta$ ), some of which are chemotactic for platelets, fibroblasts, and immune cells; interact with fibrin
      - ◆ **Fibrin** (first ECM component deposited) and **fibronectin** (helps provide a matrix for fibroblasts to rebuild) are essential to the process of clotting and coagulation
        - Important to remember that the clot must be cleared (by plasminogen/plasmin and metalloproteinases) for appropriate scar healing
    - Vasodilation caused by histamine, prostaglandins, complement, and kinins
    - **Influx of neutrophils in first 48 hours** (fibrinogen/fibrin products, C5a, and other cytokines chemoattract neutrophils)
      - ◆ Involved in clearance of bacteria and debridement
    - **Macrophages** arrive next → they are the cell type that is **ABSOLUTELY REQUIRED** for wound healing!!!
      - ◆ Phagocytose/debride tissue/organisms and set the stage for the proliferative stage (via secretion of growth factors → ↑fibroblasts and ECM development)
  - **Proliferative phase** (starts around day 5–7 and may last up to 1 month):
    - Initiated by growth factors (PDGF, TGF- $\alpha/\beta$ , FGF, and others) released by macrophages
    - Reepithelialization beginning within 24 hours, and is mediated by EGF, KGF, IGF-1, and other growth factors released by fibroblasts, platelets, and keratinocytes
      - ◆ **Keratinocytes** from sites adjacent to the wound **leapfrog** over each other (lateral mobilization 2° to breakdown of desmosomes) → reepithelialization
        - Collagenase produced by monocytes also helps with keratinocyte migration
    - Formation of granulation tissue (macrophages, fibroblasts, and vessels) at 3 to 5 days, and deposition of extracellular matrix scaffolding for repair
      - ◆ **Fibronectin needed for granulation tissue formation** → replaced by collagen III and ultimately collagen I
    - Fibroplasia at 3 to 14 days – deposition of collagen and other ECM components by fibroblasts (migrate about 2 days after wound creation; rely on fibronectin framework for migration/travel)
      - ◆ **Wound contraction mediated by myofibroblasts** (maximal at 1–2 weeks; these cells contain actin microfilaments)
    - Neovascularization/angiogenesis – mediated by VEGF, TGF- $\beta$ , angiogenin, and other molecules
      - ◆ Starts in first week of wound healing
  - **Remodeling** (starts at 3–4 weeks and can take 1 year):
    - Scar matrix formation (via fibroblast production of collagen/fibronectin/hyaluronic acid), and regression of granulation tissue (endothelial cells are first to undergo apoptosis and macrophages are last); collagen remodeling
- Scar strength (High-Yield!)
  - 1 week: up to 5%
  - 3 weeks: 20%
  - 3 months: 50%
  - 1 year: 80%

### 1.4 GENETICS

- Genetic basis of diseases can be straightforward, a single-gene defect (epidermolysis bullosa), polygenic, or only partially genetic (diabetes and psoriasis)
- Inheritance patterns: examination of family tree and its affected individuals can predict risk of future offspring to be affected (Table 1-7)



**Table 1-7.** Patterns of Inheritance

Pattern	Parents Affected	Gender Affected	Transmission	Recurrence Risk	Risk Factors
Autosomal recessive	No (carriers)	Both equally	Disease seen in siblings of proband, not in parents or offspring Usually seen in one generation	1 in 4	Consanguinity, isolated population (e.g., geographically, linguistically)
Autosomal dominant	Yes*	Both equally	Disease seen in every generation	1 in 2	<i>De novo</i> mutations
X-linked recessive	Mother a "carrier"	Males have the "full" disease Female "carriers" may have mild manifestations (e.g., in a mosaic pattern)	No male-to-male transmission (but all daughters of an affected male are "carriers")	1 in 2 male children born to a female "carrier" will be affected (and 1 in 2 of her female children will be carriers)	<i>De novo</i> mutations

\*Unless the proband has a *de novo* mutation and is therefore the first generation affected.  
(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

## 1.5 LABORATORY TECHNIQUES AND MOLECULAR BIOLOGY

- See Tables 1-8 to 1-13

## 1.6 ULTRAVIOLET LIGHT

### Ultraviolet light (Fig. 1-4)

- Ultraviolet light (UV) is made up of:
  - Vacuum UVC (10–200 nm)
  - UVC (200–280 nm)
  - UVB (280–320 nm)
  - UVA (320–400 nm) → divided into UVAII (320–340 nm) and UVAI (340–400 nm)
- Solar radiation is made up of approximately 50% visible light, 40% infrared, and 9% UVR
  - UVA is present consistently from sunrise to sunset, whereas UVB peaks around noon
- Light has properties of both waves and photons
- For light to have a cutaneous effect it must be absorbed by a chromophore of the epidermis (nucleic acid, protein, urocanic acid, and melanin) or chromophores of the dermis (hemoglobin and porphyrins)
- **Absorption spectrum:** the portion of the electromagnetic (EM) spectrum that is absorbed by a particular molecule or chromophore
- **Action spectrum:** the portion of the EM spectrum that produces a particular effect
- UVB is responsible for converting provitamin D3 (7-dehydrocholesterol) to previtamin D3, which is isomerized in the peripheral circulation to vitamin D3; **vitamin D3 is converted to 25-hydroxyvitamin D3 in the liver**
  - 90% of vitamin D produced in this manner, 10% from dietary intake
  - 25-hydroxyvitamin D3 is measured to assess vitamin D stores; **active form is 1,25-hydroxyvitamin D3 (conversion occurs in the kidneys)**

### Minimal erythema dose

- Minimal erythema dose (MED) is the minimal amount of a particular UVR that leads to minimal erythema of the exposed skin
- Typically measure 16 to 24 hours after exposure
- MEDs are important to determine the appropriate starting dose of phototherapy

### Important definitions

- Irradiance/power (watts) is the intensity of UVR to which a patient is exposed
- Exposure time (seconds) is the length of time a patient undergoes UVR treatment
- The dose ( $\text{J}/\text{cm}^2$ ) is the amount of light energy a patient is exposed to
- These three values are important for the formula: **dose ( $\text{J}/\text{cm}^2$ ) = irradiance ( $\text{J}/\text{s}.\text{cm}^2$ ) × exposure time (s)**

## 1.7 IMMUNOLOGY

### 1.7.1 Innate vs adaptive immunity

#### Innate immunity

- Initial defense with **no memory** response; present from birth; **recognize foreign antigens only** (not self-antigens)
- Pathogen-associated molecular patterns (PAMPs; conserved patterns in microorganisms) bind to pattern recognition receptors, such as **Toll-like receptors (TLRs)** and nucleotide oligomerization domain (NOD) receptors
- Activated in the first few hours after a break in the epithelial barrier
- Cells involved include granulocytes, phagocytes, dendritic cells, and NK-cells
- **Complement cascade** plays an important role in the defense against bacterial and viral infections
- Both **cathelicidins** and **defensins** are antimicrobial peptides of the innate immune system (**increased in psoriasis and decreased in atopic dermatitis**)

**Table 1-8.** Polymerase Chain Reaction**Purpose**

Amplify a specific piece of DNA from a complex mixture

**Requirements**

Need to know sequence of the DNA of interest (or at least its ends)

**Underlying concepts**

- Double-stranded DNA can be melted or unwound to single strands with increased temperature; when cooled, the single strands come back together to form double strands (hybridize) if the nucleotide sequences are complementary\*
- During the hybridization process, two complementary strands bind to each other. The A nucleotides on one strand bind to T nucleotides on the complementary strand, C nucleotides of one strand bind to G nucleotides on the complementary strand, and vice versa
- In PCR, short DNA strands called oligonucleotide primers are designed for hybridization to specific sequences in the template DNA

**Outline of method**

- Oligonucleotide primers are designed to hybridize to specific sequences at each end of the DNA of interest. These primers are added to a reaction vessel mixture containing the template DNA along with a thermostable DNA polymerase, the nucleotides dATP (A), dTTP (T), dGTP (G) and dCTP (C), and the buffer
- The reaction vessel is placed in a thermal cycler, which controls the temperature of the reaction through many cycles
- Each cycle follows these steps: **(1) denaturation; (2) primer annealing or primer hybridization; (3) primer extension; and (4) repeat** the complete cycle of PCR 30–40 times

**Benefits**

- PCR is **simple and rapid**
- Because the PCR product is exponentially increased, it is **extremely sensitive** in amplifying low amounts of DNA. Each cycle increases the number of PCR products two-fold. The total number of PCR products after  $n$  cycles will be  $2^n$

**Limitations/errors**

- Because of its high degree of sensitivity, laboratory contamination of a DNA sample by trace amounts of the PCR product can cause misleading results
- Primers used for PCR can anneal to sequences that are similar, but not identical, to the sequence of interest. This can be countered with “hot start” techniques (DNA polymerase is prevented from acting until after the first denaturation step) or nested PCR (after the PCR amplification, repeat the PCR amplification using a second set of primers that hybridize to sequences inside the first set of primers). In nested PCR, the second set of primers will only hybridize to the correct PCR products resulting from the first PCR amplification
- DNA polymerase occasionally incorporates incorrect nucleotides. For sequencing by PCR, polymerases that possess proofreading enzymatic activity can be used. This also allows the generation of even longer PCR products, up to approximately 50 kb long

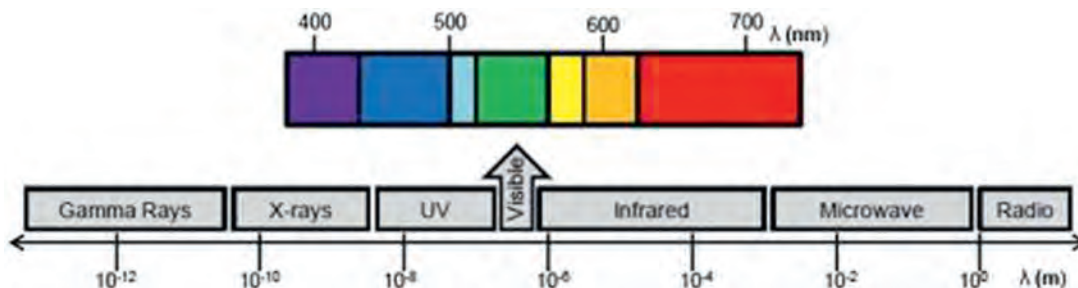
**Experimental applications**

- DNA can be amplified either for detection of a specific sequence or for cloning that sequence
- PCR can be used to label DNA with radioactive nucleotides
- PCR can be used for rapid haplotype analysis

**Modifications/alternatives**

- **Quantitative PCR** – the amount (number of copies) of a specific piece of DNA can be quantified by a variety of methods utilizing PCR. A relatively simple and high-throughput method, called real-time quantitative PCR, uses a specially designed thermal cycler that measures the amount of PCR product formed after each cycle. The higher the level of DNA, the earlier the product can be detected. This can be **used to measure genetic changes in cancer such as gene amplification**, to quantify the amount of residual cancer following treatment, or to quantify the amount of a pathogen in a sample. Modifications of this procedure allow for discrimination of gene polymorphisms
- **Southern blot, in situ hybridization**, comparative genomic hybridization

\*Hybridization actually forms the basis of several techniques in molecular biology, as the two strands can be DNA:DNA (PCR, Southern blotting), DNA:RNA (Northern blotting, in situ hybridization), or RNA:RNA. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 1-4.** Electromagnetic spectrum. (From Baron ED and Suggs AK. *Introduction to Photobiology*, 2014-07-01Z, Volume 32, Issue 3, Pages 255–266. Elsevier. 2014)

**Table 1-9.** DNA Sequencing**Purpose**

**Determine the sequence** or order of nucleotides (A, G, C, T) in a stretch of DNA

**Requirements**

The piece of DNA to be sequenced can be either a PCR product or a cloned piece of DNA present in a plasmid, but it should be pure

**Underlying concepts**

- Chain termination, or a variation thereof, is the preferred method for DNA sequencing
- In chain termination, the extension of a new strand of DNA is stopped by the addition of an analog of dATP, dCTP, dGTP, or dTTP (ddATP, ddCTP, ddGTP, or ddTTP, respectively), to the sequencing mixture. When the DNA polymerase incorporates the analog nucleotide instead of the correct normal nucleotide, DNA synthesis is terminated because the polymerase is no longer able to link to the next nucleotide
- Gel electrophoresis is used to separate the different sizes of DNA fragments that result from chain termination synthesis. The DNA fragments are forced to travel through a gel using an electric current; the smaller molecules are less impeded by the gel and travel faster than larger molecules\*

**Outline of method**

- An oligonucleotide primer hybridizes to the DNA to be sequenced and DNA polymerase synthesizes a second complementary strand
- The synthesis of the second strand is interrupted randomly by the incorporation of the fluorescent nucleotide analogs (ddATP, ddGTP, ddCTP, ddTTP), and the DNA fragments containing this final nucleotide analog can be identified because each of the four ddNTPs is labeled with a different color fluorochrome
- The different DNA fragments are electrophoresed through a polyacrylamide gel or capillary tubes
- The different lengths of DNA strands terminating with different fluorochrome-labeled nucleotide analogs pass a fluorescence detector and indicate the order of the DNA sequence

**Benefits**

- The fluorescent chain termination method is able to rapidly sequence large amounts of DNA with automated analysis of results

**Limitations/errors**

- Routinely sequence only approximately 500 bases per run
- Difficulty with G-rich and C-rich regions
- DNA must be high quality

**Experimental applications**

- Determine previously unknown sequence
- Confirm sequence following the cloning of a DNA fragment of interest and other manipulations

**Modifications/alternatives**

- Pyrosequencing
- Sequencing by oligonucleotide ligation and detection
- Solid phase amplification followed by sequencing by synthesis of randomly fragmented DNA

\*Gel electrophoresis is used in many molecular biologic techniques to separate DNA, RNA, or protein molecules of differing sizes. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 1-10.** Reverse Transcription PCR (RT-PCR)**Purpose**

- To amplify mRNA by PCR, the mRNA is first converted to DNA (called complementary DNA or cDNA), followed by PCR amplification of a specific region of the cDNA to detectable levels

**Requirements**

- Starting material can be total cellular RNA (including ribosomal, transfer, and messenger RNA [mRNA]) or purified mRNA

**Underlying concept**

- In order to facilitate studies of RNA, many techniques that study RNA first convert the RNA to cDNA with an enzyme called reverse transcriptase, an RNA-dependent DNA polymerase

**Outline of method**

- Reverse transcriptase can convert mRNA to cDNA by three different methods, depending on the primer used for the initial RT step.\* (1) Random hexamer primers contain six nucleotides (6-mer) that have all possible sequence combinations of the dA, dG, dC, and dT nucleotides ( $4^6$  possible combinations). These random hexamers will hybridize to the corresponding complementary sequences in the sample RNA. (2) Oligo dT primers contain only dT nucleotides and hybridize to the complementary string of dA nucleotides that are present at the end of mRNA molecules (poly A tail). (3) The third choice is a primer that will only hybridize to a specific mRNA sequence
- After the mRNA has been converted to cDNA, primers that can hybridize to specific sequences are added and PCR amplification is performed

**Benefits**

- As for PCR, RT-PCR is simple and rapid
- RT-PCR is **extremely sensitive in detecting low levels of mRNA transcripts**

**Limitations/errors**

- If the RNA sample is contaminated with DNA (that contains the gene of interest), a PCR product may be amplified from the DNA even though the corresponding mRNA for the gene is not present. To control for this, RT-PCR of RNA samples can be done with and without reverse transcriptase<sup>†</sup>
- **RNA is fragile** and the absence of a specific mRNA transcript may result from RNA degradation during and following extraction. RNA quality can be tested by gel electrophoresis and/or by RT-PCR of a housekeeping gene (expressed by all cells)

Continued

**Table 1-10.** Reverse Transcription PCR (RT-PCR)—cont'd

**Experimental applications**

- The mRNA gene transcripts can be amplified for subsequent cloning or sequencing
- The mRNA gene transcripts (instead of the gene) could be analyzed for the presence of mutations

**Modifications/alternatives**

- **Quantitative RT-PCR** – by adding a reverse transcription step to quantitative PCR, the levels of mRNA transcripts from genes of interest can be quantified. This is very important because it allows us to precisely **measure and compare the number of mRNA transcripts in different types of cells** or cells grown under different conditions
- Correspondingly, samples that contain less mRNA transcripts will require more PCR cycles before the exponential phase. Therefore different RNA samples can be precisely compared by measuring the number of PCR cycles (x axis) needed to produce a defined amount of PCR product (y axis)
- By carefully designing the primers, quantitative RT-PCR can be used to measure the amounts of alternatively spliced forms of a gene
- Alternative methods to measure RNA levels, not based on RT-PCR, include **Northern blots** and ribonuclease protection assays
- Differential display – this is used to find differences in gene expression in several samples. It is an RT-PCR-based system that uses short arbitrary primers that amplify numerous genes in a sample. By comparing the complex banding pattern of PCR products observed after gel electrophoresis, bands can be observed that are present in some samples but not others. With further study, these differing bands can be identified as corresponding to known or novel genes

*\*In addition to the RNA, the reaction mixture contains the reverse transcriptase enzyme, an oligonucleotide primer, dNTPs, and buffer.*

*†If DNA contamination is not present, PCR products will not be amplified from RNA that has not been reverse transcribed, and PCR products will be present only in RNA samples that have been reverse transcribed into cDNA.*

*(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)*

**Table 1-11.** Western Blot

**Purpose**

- Western blot analysis can measure the size and amount of protein present in a sample

**Requirements**

- Western blot analysis requires an antibody that is specific for the protein of interest (i.e., does not cross-react with other proteins)

**Underlying concepts**

- Polyclonal antibodies that react to several epitopes on a protein antigen are obtained by injecting a protein into an animal and later isolating the antibodies from the serum immunoglobulin fraction
- Monoclonal antibodies that react to only one epitope of a protein antigen are obtained by immunizing mice (or rats, rabbits, or chickens) with the antigen, then fusing the animal's reactive lymphocytes with an immortal myeloma cell line to create cells that are able to provide antibodies indefinitely
- A secondary antibody is used to detect the protein or the primary antibodies bound to the protein. These detection antibodies can be visualized by attaching a fluorescent probe or by attaching an enzyme that can produce either light or color by enzymatic action on a substrate

**Outline of method**

- A solubilized protein mix is separated on a polyacrylamide gel and transferred electrophoretically to a membrane. The membrane is then soaked in a buffer containing the antibody. Bound antibody is detected by a chromogenic or chemiluminescent assay

**Benefits**

- Western blot analysis is a simple and sensitive method to detect and quantify proteins present in a complex mixture
- Western blot analysis can **determine the molecular weight of a specific protein** relative to standard controls

**Limitations/errors**

- Proteins are subject to degradation during extraction. The use of protease inhibitors in the extraction buffer helps to prevent degradation
- To perform analysis by Western blot, one must possess a highly specific antibody that can recognize denatured proteins
- Western blots may contain a high background of nonspecific staining. To correct this, blocking agents such as bovine serum albumin or milk protein are used
- Large proteins transfer poorly from the gel to membrane, and small proteins may transfer through the membrane without binding. Adequate transfer to the membrane can be accomplished by controlling the duration of the transfer procedure

**Experimental applications**

- Detection, quantification, and characterization of a specific protein
- **Identification of antibody activity to a known antigen**

**Modifications/alternatives**

- Dot blot – a drop of the protein mixture is placed on a paper membrane and the protein of interest detected with antibodies, as in a Western blot. The disadvantage of this technique is that, owing to the elimination of size separation by gel electrophoresis, specific binding to the protein of correct size cannot be distinguished from nonspecific background binding to proteins
- **Immunoprecipitation (IP)** – in this technique, the specific antibody is added to the protein mixture and the resulting antibody-protein complexes are then isolated. Because proteins are not first denatured in IP, they can be detected in a more native configuration
- IP-Western – protein-protein interactions can be studied by first immunoprecipitating the protein with one antibody, bringing down a protein complex. The protein complex is then separated on a polyacrylamide gel, followed by Western blotting to detect members of the protein complex
- **Enzyme-linked immunosorbent assay (ELISA)** – this is a **sensitive and specific method for quantifying the amount of a protein**. The protein of interest is captured on a plate coated with a monoclonal antibody and other proteins are washed away. The protein is then detected using a secondary antibody that has been modified for detection using a colorimetric or luminescent assay
- **Immunohistochemistry** – this is used to visualize the cellular localization of a protein. An antibody to the protein of interest is applied to a tissue section. The antibody is detected using a secondary antibody coupled to an enzyme that reacts with a substrate to produce a colored precipitate

*(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)*

**Table 1-12.** Nucleic Acid Arrays**Purpose**

- To **profile the mRNA expression of thousands of genes** in one experiment

**Requirements**

- Total RNA or mRNA from samples (larger amounts than required for RT-PCR)

**Underlying concepts**

- Hybridization to DNA – the same principle of hybridization applies as in PCR, except that many different genes are being evaluated simultaneously. DNA is attached to beads, chemically synthesized on a surface at thousands of specific locations, or spotted onto glass slides. If cells express the mRNA of the corresponding gene, labeled cRNA prepared from mRNA in those cells will hybridize and generate a signal intensity related to its level of expression

**Outline of method**

- RNA is reverse transcribed to generate cDNA. *In vitro* transcription of the cDNA in the presence of biotinylated nucleotides yields biotin-labeled cRNA. Labeled cRNA molecules are then hybridized to small DNA fragments attached to beads or on a chip. The samples are stained with streptavidin phycoerythrin, the streptavidin binding the biotin on the cRNA and the phycoerythrin generating a fluorescent signal. Usually, the **patterns of gene expression of two samples are compared, such as normal vs tumor, or treated vs untreated**
- Alternatively, oligonucleotide arrays can be used. Using this approach, the RNA is directly labeled with either fluorescent or radioactive nucleotides, and hybridized to oligonucleotides on a slide or membrane. When using radioactive probes, the samples are hybridized to separate microarrays. If the mRNA samples to be compared are labeled with differently colored fluorescent probes, the two samples can be hybridized to the same array simultaneously
- A scanner measures the intensity of the signals at each spot and computer software determines those genes that are over- and underexpressed in one sample compared with the other

**Benefits**

- **Thousands of genes can be rapidly and quantitatively profiled in one experiment**

**Limitations/errors**

- Genes expressed at low levels may not be detected
- For some genes, the cRNA may not hybridize under the conditions used
- The RNA must be of very high quality

**Experimental applications**

- Microarray analysis can be used to profile changes in gene expression
- The patterns of gene expression can be used to group samples

**Modifications/alternatives**

- Subtractive hybridization
- Serial analysis of gene expression (SAGE)
- Deep sequencing
- MicroRNA arrays
- **Comparative genomic hybridization (CGH)** to detect differences in DNA copy number
- Single nucleotide polymorphism (SNP) arrays to assess markers of genetic variation; useful for linkage analysis, including genome-wide association studies

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

## Adaptive immunity

- Lag phase before activation and differentiation of lymphocytes in response to antigens produced from a specific pathogen → antigen-specific effector T- and B-cells are generated (via gene rearrangement)
- “Memory” is the response following reexposure to antigen → increased and rapid effector lymphocytes
- The T- and B-cell receptors **can recognize both foreign and self-antigens** (and do not distinguish between them)
  - Recognition of self-antigens can → autoimmune disease processes
- Complement has recently been identified to play a role in generation of both antigen specific T- and B-lymphocytes
- Cells involved include dendritic cells, T-, and B-cells (antibodies important in adaptive immunity)

## 1.7.2 Immunologic mediators

### Cytokines

- Cytokines bind to cellular receptors → activation or inhibition of downstream signaling pathways → modulates proliferation, function, and/or differentiation

- Have traditionally been classified into three groups (interleukins, lymphokines, and chemokines) based on their functions, cellular source, and target; however, much cross-over exists and each cytokine may have a variety of functions (pleiotropism) (Table 1-14)

### Toll-like receptors

- TLRs in humans recognize PAMPS (see [innate immunity](#) above) and are usually expressed on APCs
- Interaction between TLRs on APCs and PAMPS on pathogens → activation of APCs and presentation of pathogen-derived antigen to T-cells → forms a link between the innate and adaptive immune systems
- **Activation of TLRs → phagocytosis** of the pathogen followed by activation of a **proinflammatory environment** with secretion of cytokines and chemokines
- All TLRs except TLR3 use the **myd88 signaling pathway** following activation (Table 1-15 and Table 1-16)

## 1.7.3 Complement pathways

- Small plasma proteins found in the blood, or on cell membranes, that are usually present in an inactive state as zymogens

**Table 1-13.** Proteomics with Mass Spectrometry**Purpose**

- The proteome of a cell represents all the cellular proteins that are being expressed under a particular set of conditions. High-throughput analysis that allows investigators to rapidly and quantitatively assess the complex mixtures of proteins present in a cell at a given point in time is under development

**Requirements**

- A mixture of cellular proteins, or peptides derived from these proteins, is purified from a defined population of cells. The protein mixture may represent total cellular proteins or a subcellular fraction of proteins, depending on the isolation procedure

**Underlying concepts**

- Mass spectrometry is able to measure very precisely the size or mass of proteins, peptides, or peptide fragments by giving these peptides a positive charge (ionization) and then measuring the time required for the positively charged peptide ions to move through a tube to a detector (time-of-flight)
- The mass of the peptide ion precisely correlates to the time-of-flight, with smaller peptides moving faster (shorter time-of-flight) than larger peptide ions (longer time-of-flight)

**Outline of method**

- The first step is to reduce the complexity of the mixture of cellular proteins or peptides to be analyzed, before mass spectrometry analysis. The two main methods to separate proteins/peptides from each other are two-dimensional gel electrophoresis and/or liquid chromatography columns
- In two-dimensional gel electrophoresis, proteins are first separated (first dimension) by isoelectric focusing in a gel containing a pH gradient. The pH gradient (acidic to basic) influences the overall charge of the protein, and in isoelectric focusing, proteins migrate through the different pH levels until they reach their isoelectric point (no charge), at which point the electrical current no longer induces their migration
- Following first-dimensional separation by isoelectric focusing, these proteins are then further separated by size through a second polyacrylamide gel (second dimension), with smaller proteins moving through the gel faster than the larger ones
- After the second-dimension separation, each unique protein will be present in a distinct “spot” on the gel. This protein spot can be physically cut out of the gel and analyzed by mass spectrometry
- Liquid chromatography can be also used to separate proteins (or peptides derived from the proteins) as they flow through columns that contain different types of resins. These resins differentially bind the cellular proteins/peptides based on their ionic strength (ion exchange columns) or their relative hydrophobicity (reverse phase columns)
- After the protein mixture is bound to the liquid chromatography columns, the proteins/peptides can be eluted from the column into different fractions or aliquots and then analyzed by mass spectrometry. Many high-throughput approaches for protein analysis utilize liquid chromatography
- Mass spectrometry analysis is then performed on the separated proteins/peptides by first ionizing them to positively charged ions using lasers or the processes of electrospray ionization and nanospray ionization. Based on the time-of-flight of the charged ion, mass spectrometry can measure, record, and print out the mass/charge ratio of every peptide along with signal intensity of that peptide
- With the help of powerful computers and bioinformatics software, the peptide mass/charge ratio measurement may allow the identification of the peptide sequence and the protein that contained this peptide
- Mass spectrometry machines are now available (tandem mass spectrometry [MS/MS]) that can “ion trap” a given peptide ion and then sequence the peptide by fragmenting it into its component amino acids. Bioinformatics software can use this sequence information to search protein databases for rapid protein identification

**Benefits**

- Mass spectrometry is extremely sensitive and able to detect very small amounts of proteins/peptides
- The field of proteomics promises to provide a tremendous amount of information regarding cell biology and disease

**Limitations/errors**

- Better technology to reduce the complexity of protein/peptide mixtures and differentially separate the proteins/peptides in a high-throughput manner is being developed
- Although mass spectrometry can measure the mass of proteins/peptides very precisely, it is more difficult to measure the amount of protein/peptide quantitatively, and more robust techniques for quantification by mass spectrometry are being developed

**Experimental applications**

- Mass spectrometry can be used to determine the complete set of proteins present in a defined population of cells that are being subjected to experimental conditions
- Mass spectrometry can differentially compare the proteins in one population of cells to those in a distinct group of cells (e.g., normal melanocytes vs tumor melanoma cells)
- Because of the sensitivity of mass spectrometry analysis, it holds promise as a sensitive diagnostic tool. For example, mass spectrometry could be used for early detection of small amounts of serum proteins that are characteristic of a particular cancer or systemic disease

**Modifications/alternatives**

- Liquid chromatography can also be used to separate proteins (or peptides derived from the proteins) as they flow through columns that contain different types of resins. Many high-throughput approaches for protein analysis utilize liquid chromatography
- Multidimensional protein identification (MudPIT)
- Isotope labeling approaches for quantitative mass spectrometry, including isotope-coded affinity tag (ICAT), stable isotope labeling by amino acids in cell culture (SILAC), tandem mass tags (TT), and isobaric tags for relative and absolute quantification (iTRAQ)
- Label-free quantitative proteomics, including peak intensity-based comparative liquid chromatography-mass spectrometry (LC-MS) and spectral count-based liquid chromatography-tandem mass spectrometry (LC-MS/MS)
- Antibody protein arrays
- Reverse-capture protein microarrays
- Tissue microarrays

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Table 1-14.** Major Cytokines

Cytokine	Immune System Source	Principal Effects
IL-1 $\alpha$ , IL-1 $\beta$	Macrophages, B-cells, keratinocytes	Increased production of acute phase proteins, <b>fever</b> , lymphocyte activation, macrophage activation, $\uparrow$ leukocyte/endothelial adhesion; involved in innate immunity inflammatory responses
IL-2	T-cells	Proliferation of T-, B-, and NK-cells; <b>T-cell differentiation</b> into different subsets including memory T-cells
IL-3	T-cells	Stimulates and leads to maturation of multiple immature <b>hematopoietic</b> cell lineages
IL-4	Th2-cells	<b>Isotype switching to IgE</b> upon stimulation of B-cells; $\uparrow$ <b>Th2 cellular proliferation</b> and differentiation
IL-5	Th2-cells	<b>Eosinophil activator</b> , B-cell activation, $\uparrow$ IgA secretion
IL-6	T- and B-cells	Involved in innate immune response and neutrophil production, B-cell differentiation, and induction of acute phase proteins
IL-8	Monocytes, T-cells, keratinocytes	Chemokine $\rightarrow$ <b>neutrophil chemotaxis</b>
IL-10	Tregs, macrophages	<b>Inhibition</b> of macrophages/dendritic cells and proinflammatory cytokine production; $\downarrow$ <b>expression of IL-12/Th1 response</b> , costimulatory molecules, and class II MHC
IL-12	Macrophages, dendritic cells	<b>Activator of Th1 response</b> ; $\uparrow$ IFN- $\gamma$ /TNF- $\alpha$ production; enhances cytotoxic activity of T- and NK-cells (cell-mediated immunity); composed of <b>p40</b> and <b>p35</b> subunits (NOTE: IL-23 also has p40 subunit, but is paired with p19)
IL-15	Monocytes	Proliferation of T- and NK-cells; enhance survival of memory T-cells
IL-17	Th17 cells	Increased cytokine and chemokine production of keratinocytes and macrophages $\rightarrow$ key role in <b>psoriasis</b> pathogenesis
IL-18	Macrophages	<b>Induces IFN-<math>\gamma</math> production</b> and NK-cell proliferation
IL-22	Th2 cells, Th17 cells	Activation and proliferation of B-cells; <b>proliferation of Th17 cells</b> ; stimulation of NK-cells
IL-23	Dendritic cells, macrophages	Promotes <b>Th17 proliferation and differentiation</b> , $\rightarrow$ key role in <b>psoriasis</b> pathogenesis; composed of <b>p40</b> and <b>p19</b> subunits (NOTE: IL-12 also has p40 subunit, but is paired with p35)
TNF- $\alpha$	<b>Macrophages</b> , mast cells, lymphocytes	Activation of macrophages and T and B lymphocytes, $\uparrow$ <b>proinflammatory cytokine production</b> , leukocyte/endothelial cell adhesion, cachexia, pyrexia, induction of acute phase proteins, $\uparrow$ MHC class I production
IFN- $\alpha$	Plasmacytoid dendritic cells, macrophages	Activation of antiviral/antitumor state (antiproliferative), $\uparrow$ MHC I expression, NK-cell activation
IFN- $\beta$	Fibroblasts, plasmacytoid dendritic cells	$\uparrow$ MHC class I expression, antiviral/antitumor state (antiproliferative)
IFN- $\gamma$	T-cells, NK-cells	MHC class I and II induction, <b>macrophage activation</b> and cytokine synthesis, $\uparrow$ endothelial cell/lymphocyte adhesion, antiviral state, antiproliferative (Th1 cells) <b>Differentiation of Th1 cells</b> , isotype switching with opsonization activity, macrophage activation, increased MHC I/II expression; <b>downregulation of Th2 pathway</b>
G-CSF	Macrophages	Stimulates division and differentiation
GM-CSF	T-cells, macrophages	Proliferation of granulocyte and macrophage precursors and activators

(Adapted from Male D, Brostoff J, Roth D, Roitt I. Immunology, 8th Ed. Elsevier. 2012)

**Table 1-15.** Toll-Like Receptors

Toll-Like Receptor	Ligand/Key Facts
TLR1	Lipopeptides from gram-negative bacteria and mycobacteria can dimerize with TLR2
TLR2	Lipopeptides from gram-positive bacteria ( <b>activated by <i>Propionibacterium acnes</i></b> ); bacterial <b>lipopolysaccharide (LPS) binding is dependent on TLR2</b>
TLR3	<b>Viral dsRNA</b>
TLR4	LPS of gram-negative bacteria
TLR5	<b>Flagellin</b> (bacterial)
TLR6	Lipopeptides (mycobacterial)
TLR7	Viral ssRNA/synthetic ligand <b>imiquimod</b> activates IFN- $\gamma$ production
TLR8	Viral ssRNA
TLR9	Unmethylated CpG DNA (bacterial)

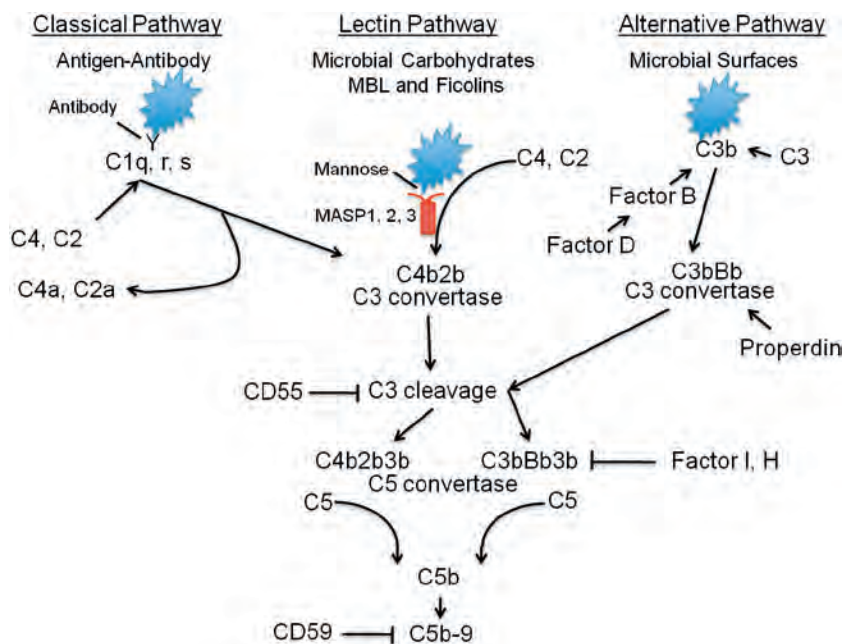
(Adapted from Male D, Brostoff J, Roth D, Roitt I. Immunology, 8th Ed. Elsevier. 2012)



**Table 1-16.** Antimicrobial Peptides

Name	Cellular Source	Antimicrobial Activity	Inducibility	Disease Implications
Antileukoprotease (ALP)	Keratinocytes airway epithelia	Bacterial and fungal	–	↑in psoriasis
Dermcidin (DCD)-1	Sweat glands	Bacterial and fungal	–	↓in atopic dermatitis
Human $\beta$ -defensin (HBD)-2	Keratinocytes airway epithelia, intestinal tract	Bacterial and fungal	+	<b>↑in psoriasis</b> <b>↓in atopic dermatitis</b>
HBD-3	Keratinocytes airway epithelia	Bacterial and fungal	+	↓in atopic dermatitis
HBD-4	Keratinocytes airway epithelia (mRNA)	Bacterial and fungal	+	–
LL-37/cathelicidin	Keratinocytes airway epithelia, urogenital tract granulocytes	Bacterial and fungal	+	<b>↑in psoriasis</b> , rosacea, condyloma acuminatum, verruca vulgaris
Lysozyme	Keratinocytes airway epithelia	Bacterial	–	–
Psoriasin	Keratinocytes sebocytes	Bacterial and fungal	+	↑in psoriasis
RNase 7	Keratinocytes airway epithelia	Bacterial and fungal	+	

(Adapted from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



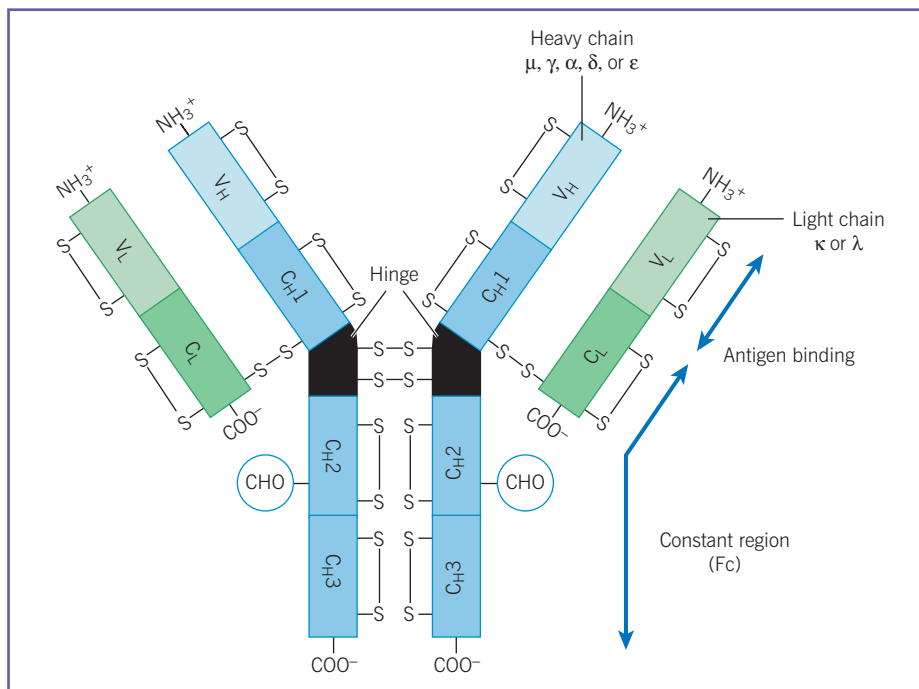
**Figure 1-5.** Complement activation pathways. The classical complement cascade is activated by antibody bound to microbial surfaces, which is a binding site for the C1 complex. The alternative pathway is activated by the binding of spontaneously generated C3b to microbial surfaces. Microbial bound C3b binds factor B, which is converted to factor Bb, forming C3 convertase. The lectin pathway is activated by the binding of MBL to mannose residues on microbial surfaces. MBL binds MBL-associated serine proteases, which bind and cleave C4 and C2, forming C3 convertase. (From Rich RR et al. *Clinical Immunology*, 4th ed. Saunders. 2013)

- Upon activation, they have serine protease activity that leads to either cleavage or activation of the subsequent protein in the complement cascade
- Complement has a number of important functions
  - **Direct lysis** of bacteria
  - **Opsonization** of bacteria (complement binds to an organism and augments phagocytosis)
  - **Chemotaxis**
  - Clearing immune complexes (hence, complement deficiency syndromes are a/w increased risk of lupus)
  - Activating immune responses
  - Anaphylaxis
- Amplification occurs at each step, as one active complement protein can activate numerous zymogens
- The complement proteins play an important role in both arms of the immune system (innate and adaptive)
- Most complement proteins are synthesized in the liver and also are acute phase reactants
- **Three complement pathways:** 1) classical pathway, 2) alternative pathway, and 3) lectin/mannose-binding pathway all lead to the formation of the membrane attack complex (MAC), C5b to C9 (Fig. 1-5)
  - MAC forms a transmembrane channel/pore in the pathogenic organism's cell membrane → lysis/death
- **Classical pathway**
  - **Activated by immune (antibody-antigen) complexes**
  - C1 has three protein subunits: C1q, C1r, and C1s
    - C1q binds to the Fc portion of the antigen-bound antibodies: IgM or IgG (IgG3 > IgG1 > IgG2; IgG4 does NOT activate classical complement pathway) → activated C1r/s
    - Activated C1s → activation/cleavage of C4 and then C2, forming **C3 convertase** (C4b/C2a)
  - C3 convertase cleaves C3 into C3a (anaphylotoxin that also enhances vascular permeability) and C3b (opsonin – binds to pathogens → phagocytosis)

- C3b and C4b2b join to form **C5 convertase**
- C5 convertase cleaves C5 into C5a (neutrophilic chemotactic factor and anaphylotoxin) and C5b
- C5b, C6, C7, C8, and C9 bind together to form the MAC
- Alternative pathway
  - Recognizes **microbial cell surface structures** without antibodies (e.g., LPS in gram-negative bacteria) → low levels of C3 cleavage
  - C3b binds bacterial cell surface structures and binds **factor B**, which is subsequently cleaved by **factor D** → Ba and Bb → Bb and C3b form the **C3 convertase (stabilized by properdin)** with subsequent steps similar to the classical pathway
  - Factor H is a regulatory protein that inhibits formation of C3 convertase
- Lectin pathway
  - Activated by **mannose-binding lectin protein** (without antibodies), which is a plasma protein
  - Mannose-binding protein (has mannose-associated serine proteases) binds to cell's surface polysaccharides (via pattern recognition) on various bacteria/fungi/viruses/protozoa → cleavage of C4 and C2 → then follows a pathway similar to the classical pathway
- **Important players in the complement pathways**  
(Adapted from Structural and functional homologies in complement pathways. Clinical Immunology, Fourth Edition Rich, Robert R., Chapter 20)
  - Recognition: C1q, mannose-binding lectin (MBL), and ficolins
  - Initiating enzymes: C1r, C1s, MBL associated serine protease (MASP)-1, MASP-2, factor-Df, and C3 convertases C4b2b and C3bBb
  - C5 convertases: C4b2b3b and C3bBb3b
  - Enzyme subunits of convertases: C2b and Bb
  - Assembly subunits: C3b, C4b, and C5b
  - **Anaphylatoxins: C3a and C5a**
  - **MAC subunits: C5b, C6, C7, C8, and C9**
  - Regulatory proteins: C4BP, factor H, complement receptor 1, complement receptor 2, and membrane cofactor protein
- **B-lymphocytes isotype switch** (can switch from one antibody class to another) if they interact with **T-helper cells (IgM to IgG, IGA, or IgE)**
- Can also present antigen in context of MHC class I to T-cells
- **Initial exposure** to antigen leads to a primary immune response:
  - Has lower antibody production (**typically IgM** with a lower-affinity antibody)
  - Some B-cells differentiate into memory B-cells or plasma cells
- **Subsequent exposure** leads to a secondary immune response:
  - **Memory B-cells** more rapidly develop into plasma cells
  - ↑**High-affinity antibody** production (IgA, IgE, and IgG)
  - ↑**Isotype switching** in the presence of helper T-cells, CD40 ligand, and other cytokines
- **B-cell markers/receptors:** FC receptor, MHC class II, various complement receptors, **CD19, CD20, and CD79a**
- Antibody structure has two identical heavy and two identical light chains with variable and constant domains that are connected by disulfide bonds. The **variable region (Fab)** has a **unique/specific antigen-binding domain**. The constant region (Fc) interacts with cell surface receptors → complement activation. Of note, papain cleaves antibody into two Fab fragments and one Fc fragment (**Fig. 1-6, Table 1-17 and Table 1-18**)
- T-cells (majority of lymphocytes)
  - Derived from the bone marrow, but mature in the **thymus**; reside in paracortex of lymph nodes
  - Stimulation → cytokine release or cell lysis
  - **Primary stimulation:** T-cell receptor recognizes the antigen only when it is complexed with MHC class I/II molecules (see Page 24 1.7.5 Major histocompatibility complex)
  - **Costimulation:** in addition, costimulatory signals between receptors and ligands present on the cell surface of the T-lymphocytes and APCs are necessary:
    - **CD28** on T-cells binds to **B7-1 and B7-2** on APCs
    - **CD2** on T-cells binds to **LFA-3** on APCs
    - **LFA-1** on T-cells binds to **ICAM-1** on APCs
  - Signaling pathways can also be inhibitory
    - **CTLA-4** expressed on T-lymphocytes binds to B7-1 and B7-2 on APCs → inhibition
    - Clinical relevance: ipilimumab blocks the CTLA-4 signaling pathway → enables greater T-cell activation and antitumor activity
  - IL-2 is produced after T-cell activation and leads to proliferation of antigen-specific T-cells
  - A subset of T-cells become memory T-cells
  - Markers include: CD2, CD3, CD4 (on helper T-cells), and CD8 (on cytotoxic T-cells)
  - T-cells are divided into CD4<sup>+</sup> T-helper cells (Th1, Th2, Th17, and Treg) and CD8<sup>+</sup> cytotoxic T-cells
    - T-helper 1 (Th1) cells

### 1.7.4 Cells of significance

- There are three main cell type families that play an important role in the adaptive phase of the immune response, which results in the generation of cytotoxic T-cells, CD4 T-helper cells, Th17 T-cells, and antibodies
  - Lymphocytes: T-cells, B-cells, and NK-cells
  - Monocytes: dendritic cells, LCs, and macrophages
  - Granulocytes: mast cells, eosinophils, and neutrophils
- B-cells
  - B-lymphocytes are formed from pluripotent progenitor stem cells in the bone marrow
  - Located in lymphoid follicle of lymph node
  - Main function is **antibody production and differentiation into plasma cells** (requires surface immunoglobulin receptors to bind antigen)



**Figure 1-6.** Antibody structure and functional domains. The basic structure of the antibody contains heavy chains and light chains, showing intradisulfide and inter-disulfide bonds and the characteristic hinge region. The interactions between variable domains constitute the antigen-binding domain, and the constant regions confer specific biologic properties of the molecule. CHO, carbohydrate. (From Actor J.A. Elsevier's Integrated Review Immunology and Microbiology, 2nd ed. Elsevier. 2012)

**Table 1-17.** Immunoglobulin Class

Isotype	IgM	IgD	IgG	IgE	IgA
Structure	<b>Pentamer</b>	Monomer	Monomer	Monomer	Monomer, dimer
<b>Complement activation</b>	<b>Strong</b>	No	<b>Yes, except IgG4</b>	No	No
Bacterial toxin neutralization	Yes	No	Yes	No	Yes
Antiviral activity	No	No	Yes	No	Yes
Binding to mast cells and basophils	No	No	No	<b>Yes (→ release of mediators)</b>	No
Additional properties	Promotes bacterial opsonization but does not opsonize itself <b>1st antibody in primary immune response</b> Does not cross placenta	Surface receptor on B-cells	Antibody-dependent cell cytotoxicity <b>Only antibody that crosses the placenta</b>	<b>Allergic/atopic responses, helminthic responses</b>	Active as dimer on epithelial/mucosal surfaces

• Antibodies bind to antigens → neutralization → opsonization or death. **Antibody classes (e.g., IgD vs IgA) are determined by the heavy chain.**

(Adapted from Actor JK, Elsevier's Integrated Review Immunology and Microbiology, 2nd ed. Elsevier-Saunders. 2011.)

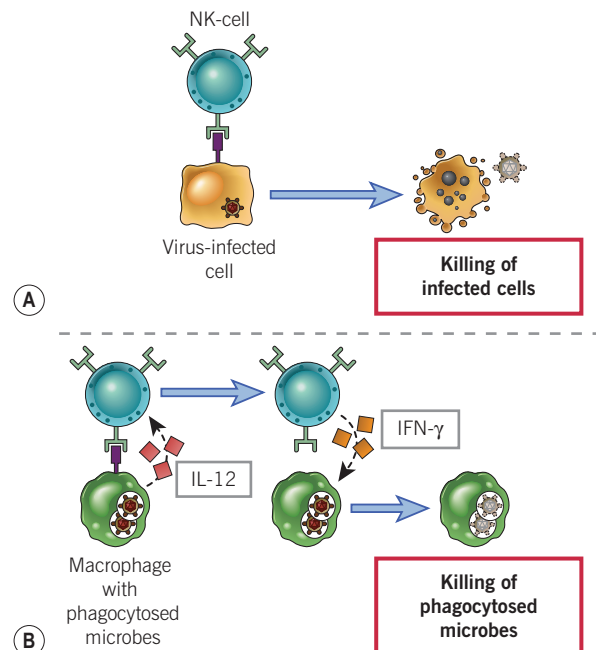
**Table 1-18.** Properties of IgG Subclasses

IgG Subclasses	IgG1	IgG2	IgG3	IgG4
Occurrence (% of total IgG)	70	20	7	3
Half-life (days)	23	23	7	23
<b>Complement binding</b>	+	+	Strong	<b>No</b>
Placental passage	++	±	++	++
Opsonizing	+	No	+	No
<b>Neutralizing</b>	No	+	No	+
Receptor binding to monocytes	Strong	+	Strong	±

(Adapted from Actor JK, Elsevier's Integrated Review Immunology and Microbiology, 2nd ed. Elsevier-Saunders. 2011.)

- ◆ Activated by intracellular pathogens → activate macrophages → response is mediated by macrophage activity
- ◆ Important in maintaining **cell-mediated immunity** and are involved in delayed-type hypersensitivity reactions
- ◆ Th1 differentiation requires stimulation by **IL-12** and **IFN-γ**, which activate the transcription factors T-bet, STAT1, and STAT4
- ◆ Th1 cells produce **IFN-γ** (downregulates Th2 pathway), **IL-2** (→ ↑T-cells/B-cells/NK-cells), **IL-12**, and **TNF-α**
- ◆ Stimulate IgG2 and IgG3 class switching
- ◆ Promote phagocytic activity through:

- IFN- $\gamma$ -mediated macrophage activation
- Fc $\gamma$ RIII cross-linking
- Complement deposition
- Opsonization
- Th2 cells
  - ◆ Th2 cells **activate eosinophils**, which help mediate systemic immune responses against helminthic parasites, and downregulate macrophage activity (IL-10 → ↓MHC II expression on APCs)
  - ◆ Important in **humoral immunity**
  - ◆ IL-4 is a key cytokine that stimulates Th2 proliferation by activating the transcription factors STAT6 and GATA-3
  - ◆ Produce IL-4, IL-5, IL-6, IL-10 (suppresses Th1 response), and IL-13 (like IL-4, important in allergies)
  - ◆ Stimulate IgG4 and IgE class switching
  - ◆ Response mediated by mast cells and eosinophils
  - ◆ Increase degranulation through:
    - Fc $\epsilon$ RI cross-linking
    - IL-5-mediated eosinophil activation
- Th17 cells
  - ◆ Th17 cells are dependent on activation of the transcription factors ROR $\gamma$ T, STAT3 (**mutated in Job's syndrome**), and TGF- $\beta$
  - ◆ Th17 cells typically recruit neutrophils that can destroy extracellular pathogens
  - ◆ Produce IL-6, IL-17, IL-22 (→ ↑ keratinocytes), IL-23 (essential for survival/division of cells), IL-36, and TNF- $\alpha$
  - ◆ Activate local endothelium
  - ◆ Induce cytokine and chemokine production
  - ◆ Increase infiltration by neutrophils
  - ◆ Activate cell-mediated inflammation
- Treg cells
  - ◆ downregulate immune response (as name suggests); express CD25 and transcription factor FOXP3
- CD8<sup>+</sup> T-cells
  - ◆ CD8<sup>+</sup> T-cells can become functional cytotoxic T-cells, with cytotoxic granules, or memory T-cells
  - ◆ They require, in some instances, activation from Th1 cells and Th1 cytokines
  - ◆ CD8<sup>+</sup> T-cells **recognize cytoplasmic antigens** when bound to MHC class I
  - ◆ Kill via the perforin/granzyme pathway
    - Perforin enables granzyme to enter the cytoplasm of virally infected cells → subsequent initiation of apoptotic pathways
  - ◆ Additionally, **Fas ligand** on CD8<sup>+</sup> T-cells binds Fas on target cells → cell death
  - ◆ Immune modulation
    - Inflammatory cytokine production, including IFN- $\gamma$  and TNF
    - Chemokine secretion
- Other T-cell subsets
  - ◆  $\gamma/\delta$  T-cells have  $\gamma/\delta$  T-cell receptor (rather than predominant  $\alpha/\beta$ )
    - Suppress Th1 system via IL-10
  - ◆ Lymphomas of the  $\gamma/\delta$  type are highly aggressive!
- Disease associations
  - ◆ Th1: multiple sclerosis, psoriasis, type 1 diabetes mellitus, **tuberculous** leprosy, cutaneous leishmaniasis, sarcoidosis, **delayed-type hypersensitivity reactions**, and CTCL (non-Sezary)
  - ◆ Th2: **atopic dermatitis**, helminthic infections, **leprous** leprosy, disseminated leishmaniasis, Sezary syndrome, scleroderma, and systemic lupus
  - ◆ Th17: asthma, multiple sclerosis, **psoriasis**, rheumatoid arthritis, transplant rejection, and allergic contact dermatitis
  - ◆ Th22: psoriasis and wound healing
- NK-cells
  - Key component of the **innate immune system**
  - Lack T-cell receptors or immunoglobulins
  - Cell surface markers include CD2, **CD56**, and CD16
  - Identify infected (viral) or tumor cells that have decreased MHC I surface expression and destroy these cells via perforin/granzymes
  - **Secrete IFN- $\gamma$**  that can enhance the phagocytic capability of macrophages and have cytoplasmic granules that have a similar mechanism to cytotoxic T-lymphocytes
  - NK-cells are activated by IL-12, IL-15, and type I interferons
  - Work synergistically with macrophages (**Fig. 1-7**)
- Mononuclear phagocytes
  - Monocytes (in bloodstream) and macrophages (in tissue) represent different stages of a cell from the



**Figure 1-7.** Functions of NK-cells. (A) NK-cells kill host cells infected by intracellular microbes, thus eliminating reservoirs of infection. (B) NK-cells respond to IL-12, produced by macrophages, and secrete IFN- $\gamma$  to activate macrophages and kill phagocytosed microbes. (From Abbas A, Lichtman AH, Pillai S. Basic Immunology 4th ed. Elsevier. 2014)



- same lineage; dermal dendrocytes are another type of mononuclear cell
- Derived from a common CD34+ progenitor cell in the bone marrow
- Cell markers: CD11a/b/c, CD6, Fc receptor for IgG, and MHC II (for antigen presentation)
- Macrophages have several key functions:
  - **Antigen presenting cells**
  - Cytokine production → modulation of inflammation
  - Tissue remodeling, **wound healing** (absolutely required), and coagulation
- Macrophages ingest pathogens into phagosomes, followed by fusion with lysosomes to form phagolysosomes, and finally pathogen destruction by reactive oxygen/nitrogen species and proteolytic enzymes
- **Eosinophils**
  - Bone marrow derived
  - Important role in defense against parasitic/helminth infections and allergic disease
  - Weakly phagocytic
  - **Activated by IL-5**
  - For helminths, initially there is **activation of Th2 cells with increased production of IL-4 and IL-5**, leading to elevated levels of IgE
  - IgE coats helminths by binding to the FcE receptor on bound eosinophils, leading to their degranulation
  - Cytoplasmic granules containing **major basic protein** (→ degranulation of mast cells/basophils), eosinophilic cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin
  - Numerous eosinophil-derived mediators:
    - Lipid mediators usually derived from arachidonic acid (leukotriene)
    - Cytokines (VEGF, GM-CSF, and IL-4)/chemokines (RANTES and Mip-1alpha)
    - Oxidative products (superoxide)
- **Mast cells**
  - Bone marrow derived from progenitor cells expressing CD34/c-kit/CD13
    - Also stain with Giemsa, toluidine blue, and Leder
  - Mast cells express high levels of **c-kit receptor** (CD117) and its ligand, **stem cell factor**, which are critical for the survival and proliferation of mast cells
  - Typically located in papillary dermis
- Important in **immediate-type hypersensitivity reactions** (e.g., anaphylaxis, urticaria, and angioedema)
- Mast cells express high levels of FcεRI (high-affinity receptor for IgE)
- Mast cell degranulation triggers: **cross-linking of FcεRI-bound IgE**, anti-FcεRI antibodies, stem cell factor, neuropeptides (e.g., substance P), drugs (opiates, aspirin, vancomycin, curare, and polymyxin B), C5a anaphylatoxin, and radiocontrast media
- Mediators (**Table 1-19**)
- **Neutrophils**
  - Highly abundant myeloid cell type; short-lived and produced in the bone marrow
  - First cells to arrive at acute inflammatory sites (neutrophil chemotactic factors include c5a, IL-8, LTB4, kallikrein)
  - Function to destroy microbial pathogens (**phagocytosis** followed by oxidation (via ROS) → death)
  - The cytoplasm contains four granule types.
    - **Primary granules** (azurophilic) containing defensins, myeloperoxidase (along with NADPH oxidase, **creates ROS** → oxidation of engulfed organisms → death; of note, defect in NADPH oxidase → chronic granulomatous disease and negative nitroblue tetrazolium test [cannot turn color from yellow to blue]), lysozyme, proteinase-3, cathelicidin, and cathepsin B/D
    - **Secondary granules** (specific) containing lactoferrin, lysozyme, alkaline phosphatase, collagenase, and phospholipase A
    - Gelatinase-containing granules
    - Secretory granules containing receptors that enhance the ability of neutrophils to respond to inflammatory signals
- **Langerhans cells**
  - Bone marrow-derived dendritic cells that are dependent on transforming growth factor-β1 (TGF-β1) and macrophage colony-stimulating factor receptor (M-CSFR) ligands for development
  - LCs usually not visualized during routine histologic analysis, and on electron microscopy have rod-shaped organelles (**Birbeck granules**)
  - **Langerin is a very sensitive and specific immunohistochemical marker** for LCs, because it

**Table 1-19.** Mast Cell Mediators

Mediator	Function
<b>Preformed and stored in granules</b>  <b>Histamine</b> Heparin <b>Tryptase</b> Chymase Cathepsin G Carboxypeptidase	Vasodilation, smooth muscle cell contraction, tissue edema Anticoagulant, controls function of other mediators Production of C3a and bradykinin, increased fibroblast proliferation Increased mucous secretion Protease Protease
<b>Major lipid mediators – newly formed</b>  <b>Prostaglandin D 2</b> <b>Leukotrienes</b> C4, D, E4 Platelet-activating factor	Bronchoconstriction, leukocyte chemotaxis, dendritic cell activation Bronchoconstriction, dendritic cell recruitment and activation Vasoconstriction
<b>Cytokines – newly formed</b> IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, TNF-α	See <a href="#">cytokine</a> section

(Adapted from Bradding P, Saito H, et al. *Middleton's Allergy: Principles and Practice* 7th ed. Elsevier. 2009.)

stains Birbeck granules; CD1a is also a fairly specific marker

- LCs are poorly phagocytic, but are **professional APCs**
- LCs are S100+, langerin (CD207)+, vimentin+, and CD1a+; adhere to keratinocytes via E-cadherin
- **Following antigen uptake, LCs move to the lymph nodes where MHC-bound antigen is presented to T-lymphocytes followed by subsequent activation of T-lymphocytes**

### 1.7.5 Major histocompatibility complex

- MHC locus in humans is known as the human leukocyte antigen (HLA) locus
- The MHC locus is found on **chromosome 6**, and its key role is to present antigen to T-cells
- Divided into three classes: MHC class I, MHC class II, and MHC class III (encodes for complement molecules)
- Typically T-cells only recognize peptides in the presence of MHC molecules
- MHC genes are codominantly expressed
- During immune activation, the expression of MHC genes is increased in response to the surrounding cytokine milieu
  - MHC class I molecules **present antigens (endogenous peptides) to CD8<sup>+</sup> T-cells**, and have the **ability to induce apoptosis** in both virally infected and tumor cells
    - Expressed on **all nucleated cells**
    - Peptide size bound by MHC class I is 8 to 10 residues
    - **Intracellular proteins** are processed by proteasomes into cytosolic peptides that are transported to the endoplasmic reticulum, followed by binding to MHC class I on the surface
    - Three main MHC I genes: HLA-A, HLA-B, and HLA-C
  - MHC class II molecules present antigens (exogenous peptides) to helper T-cells
    - Expressed on **APCs** (i.e., monocytes, macrophages, dendritic cells, B-lymphocytes, and activated T-lymphocytes)
      - ◆ Not expressed on plasma cells
    - Peptide size bound by MHC class II is 10 to 34 residues
    - Endocytosis of **extracellular antigens** into vesicles where the antigens are processed, peptides loaded on class II MHC molecules, and expressed on the surface
    - Three main MHC II genes: HLA-DP, HLA-DQ, and HLA-DR
- **MHC-associated diseases (High-Yield exam factoids!):**
  - Lupus (SLE and SLE): HLA-DR3
  - Psoriasis: HLA-Cw6 (most linked to psoriasis), B17 and B13 (guttate psoriasis), and B27 (psoriatic arthritis)
  - Reactive arthritis: HLA-B27
  - Behçet's disease: HLA-B51
  - Chronic idiopathic urticaria: HLA-DR4, HLA-DRB4, and HLA-DQ8

- Pemphigoid gestationis: HLA-DR3 and HLA-DR4
- Pemphigus vulgaris: HLA-DR4 and DRw6
- Dermatitis herpetiformis: Class I: HLA-A1 and HLA-B8; Class II: HLA-DR3 and HLA-DQ2
- Lichen planus: Class I: HLA-B57 and HLA-B8; Class II: HLA-DR1 and DR10
- Vitiligo: Class I: HLA-A33 and HLA-B13; Class II: HLA-B44, HLA-DRB1, and HLA-DR4

### FURTHER READING

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# Dermatopharmacology

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## 2.1 ANTIHISTAMINES

### Mechanism of action (MoA)

- H1 and H2 antihistamines are inverse agonists (downregulate constitutively activated state of receptor) or antagonists at histamine receptors
- Histamine levels are elevated in the skin of chronic urticaria; itching is largely histamine-mediated (H1 receptors, but NOT H2 receptors)
  - H1 antihistamines are primarily used in dermatology
    - Good for urticaria and some cases of eczema, but not as monotherapy
  - H2 antihistamines can be added for chronic urticaria, but evidence is poor

### Important facts

- H1 antihistamines are likely safe in pregnancy, but none are FDA category A – diphenhydramine or chlorpheniramine may be best choices if needed because of their long safety record; also appear safe in lactation
- Best for urticaria and angioedema, but likely not a great option for atopic dermatitis (though first-generation H1 antihistamines may be helpful for itching at night)

### First-generation H1 antihistamines

- Adverse effects: **sedation**, impaired cognitive function (from lipophilicity; cross blood-brain barrier), and **anticholinergic effects** (dry mouth, constipation, dysuria, and blurred vision)
- Metabolized by cytochrome P-450 system

- Examples: diphenhydramine (pregnancy category B), cyproheptadine (interferes with hypothalamic function → may ↑ appetite and retard growth in children), promethazine, chlorpheniramine (pregnancy category B – long track record of safety), and hydroxyzine

### Second-generation H1 antihistamines

- **Less sedating** (because of ↓ ability to cross blood-brain barrier) and **lack anticholinergic effects**
- Appear to be relatively equivalent for dermatologic indications (e.g., chronic urticaria)
- Fexofenadine: active metabolite of the prodrug terfenadine (which was withdrawn because of Q-T elongation and torsades de pointes); not metabolized by the liver and excreted unchanged
- Loratadine: ↓ dose in patients with hepatic or renal impairment; pregnancy category B
- Cetirizine: carboxylic acid metabolite of hydroxyzine, mainly excreted unchanged; ↓ dose in patients with hepatic or renal impairment; >10% get drowsiness (**most sedating** of second-generation antihistamines); pregnancy category B
- Desloratadine: active metabolite of loratadine, 5× more potent than loratadine in suppressing histamine wheal
- Levocetirizine: active metabolite and R-enantiomer of cetirizine

### Other antihistamines

- Doxepin: tricyclic antidepressant with H1 and H2 antihistamine activity; effective in urticaria and depressed patients with neurotic excoriations; available orally and

topically (5% cream – can cause allergic contact dermatitis and drowsiness)

- Much higher affinity for histamine receptors than most antihistamines
- Therapeutic effect longer lasting than diphenhydramine and hydroxyzine because of long half-life (thus QHS dosing)
- Sedation is most common side effect (SE); others include anticholinergic SEs and orthostatic hypotension
- Do not give with other antidepressants, or with severe heart disease (risk of heart block)
- Can ↓seizure threshold
- Can induce manic episodes in patients with manic-depressive disorder
- Black box warning for suicidality

## 2.2. RETINOIDS

### Introduction

- Vitamin A and related natural and synthetic compounds are known as retinoids
- Three interconvertible forms: retinol (alcohol), retinal (aldehyde), and retinoic acid (acid)
- Acquired through diet (dairy, fish, meat, eggs, leafy greens, and orange/yellow vegetables)
  - Carotenoids (beta-carotene) are precursors of vitamin A
- Stored in the liver as retinol
- Retinol is transported in plasma by binding to a complex of retinol binding protein and transthyretin

### Mechanism

- Binds cytosolic retinoid binding protein → transported to the nucleus → binds intracellular nuclear receptors
- Binds to two families of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs)
  - Each receptor family contains 3 isotypes ( $\alpha$ ,  $\beta$ , and  $\gamma$ )
  - Different retinoids bind to different receptors
  - The major receptors in keratinocytes are RXR- $\alpha$  and RAR- $\gamma$  (most abundant in skin)
    - Photoaging → ↓RXR- $\alpha$  and RAR- $\gamma$
    - Topical retinoids → ↑stratum corneum thickness, epidermal hyperplasia, correction of atypia, dispersion of melanin granules, ↑dermal collagen I, ↑papillary dermal elastic fibers, ↑hyaluronic acid, ↓matrix metalloproteinases, and ↓angiogenesis
- Binding to RAR/RXR affects various genes and transcription factors that are involved in many functions (cellular proliferation, differentiation, embryonic development, cellular cohesiveness, and inflammatory effects)
  - Inhibits AP1 and NF-IL-6, which are important in proliferation and inflammatory responses
  - Inhibits TLR2, which is important in inflammation
  - ↓tumorigenesis and induces apoptosis
  - Antikeratinization (downregulates K6 and K16)
  - Inhibits ornithine decarboxylase

- ↑TH1 cytokines and ↓TH2 cytokines (helpful in CTCL) (Table 2-1 and Table 2-2)

## Side Effects (SEs) of systemic retinoids

### Mucocutaneous

- Earliest and most common SE is cheilitis (dry lips)
- Thirst, dry nasal mucosa, epistaxis, xerosis, xerophthalmia, palmoplantar peeling, photosensitivity, exacerbation of eczema, and *Staphylococcus aureus* colonization in isotretinoin patients (75%–90%; as a result of dryness of the nasal mucosa), telogen effluvium, nail fragility, pyogenic granuloma-like lesions, and sticky sensation (palms and soles)

### Systemic

- Myalgias, arthralgias, anorexia, nausea, diarrhea, abdominal pain, IBD (controversial), headache, pseudotumor cerebri (esp. if used in conjunction w/ tetracyclines), fatigue, reduced night vision, questionable depression/suicidal ideation, hepatitis, pancreatitis secondary to hypertriglyceridemia, rarely bone toxicity (diffuse idiopathic skeletal hyperostosis [DISH]; more common with acitretin), calcification of tendons and ligaments, and premature epiphyseal closure

### Labs

#### Hyperlipidemia/hypertriglyceridemia

- Most common laboratory abnormality, highest risk w/ bexarotene
- Discontinue if fasting TGs >800 mg/dL because of a pancreatitis risk

#### Elevated LFTs

- Usually transient within 2 to 8 weeks of starting treatment, return to normal after another 2 to 4 weeks of treatment
- If elevations are greater than 3× the upper limit of normal, should discontinue
- More frequent with acitretin than isotretinoin or bexarotene

#### Central hypothyroidism

(occurs in 80% on bexarotene)

- Decreased TSH and T4
- Is reversible
- Current recommendations are to start low-dose levothyroxine in all patients

#### Leukopenia (neutropenia) and agranulocytosis (bexarotene >> others)

### Teratogenicity

- 50%–60% of isotretinoin-exposed pregnancies result in “healthy-appearing” births (lack obvious retinoid embryopathy)
  - However, ↓mental function becomes apparent in majority of these children over time: 30% have gross mental retardation and 60% have mild-moderate mental deficits

**Table 2-1.** Topical Retinoids

Retinoid	Generation	Systemic Absorption (% Dose)	Timing of Improvement	Pregnancy Category	Nuclear Receptor Profile	Uses/Treatment Indications	Side Effects	Miscellaneous
Tretinoin (all- <i>trans</i> -RA)	First (nonaromatic)	1%–2% in normal skin	8–12 weeks	C	All RAR	Acne, photoaging, (hyperpigmentation, AKs on face, disorders of keratinization, and striae)*	Irritation, erythema, peeling, pruritus, photosensitivity, and temporary worsening of acne	<b>Inactivated by UV</b> → apply at night <b>Oxidized by benzoyl peroxide</b>
Alitretinoin (9- <i>cis</i> -RA)	First	Not measurable	4–8 weeks	D	All RAR and RXR	<b>Kaposi</b> sarcoma	Irritation, erythema, and pruritus	" <b>AL(L)</b> itretinoin binds <b>ALL</b> forms (RARs and RXR) of receptors"
Adapalene	Third (poly aromatic)	Trace amounts	8–12 weeks	C	RAR- $\beta/\gamma$ > $\alpha$	Acne (photoaging and hyperpigmentation)	Irritation, erythema, peeling, and pruritus	<b>Light stable</b>
Tazarotene	Third	<5% in normal skin	8–12 weeks	<b>X</b>	RAR- $\beta/\gamma$ > $\alpha$	Acne and plaque psoriasis (photoaging, hyperpigmentation, disorders of keratinization, and AKs)	Irritation, erythema, peeling, and pruritus	
Bexarotene	Third	Trace amounts	20 weeks	<b>X</b>	All RXR	<b>CTCL</b> (stage 1A and 1B), (LyP, hand dermatitis, psoriasis, and alopecia areata)	Irritation and erythema	"be <b>X</b> arotene = <b>RXR</b> "
Retinol	Precursor of RA		8–12 weeks			Cosmeceutical product, photoaging, and hyperpigmentation	Less irritation	
Retinaldehyde	Precursor of RA		8–12 weeks			Cosmeceutical product, photoaging, and hyperpigmentation	Less irritation	

\*Off-label uses listed within ( )  
RA = retinoic acid

- Most common adverse results in pregnant patients exposed to isotretinoin:
  - Spontaneous abortion (20%)
  - **Retinoid embryopathy** (18%–28%): craniofacial, cardiac, CNS, and thymic abnormalities are most common

#### Specific features of RE:

- **Craniofacial:** microtia, cleft palate, microphthalmia, hypertelorism, dysmorphic facies, and ear abnormalities
- **CNS:** microcephaly, hydrocephalus, CN7 palsy, and cortical and cerebellar defects
- **CV:** cardiac septal defects, tetralogy of Fallot, transposition of great vessels, and aortic arch hypoplasia
- **Thymic:** thymic aplasia/ectopia
- No risk of retinoid embryopathy reported in male partners taking retinoids; however, iPledge requires male registration because pregnancies have been reported where women have "borrowed" their male partner's medication

### Contraindications

- Absolute: pregnancy, women contemplating pregnancy, noncompliance with contraception, breastfeeding,
- hypersensitivity to parabens (some capsules may contain parabens)
- Relative: leukopenia, moderate to severe hypercholesterolemia or hypertriglyceridemia, significant hepatic or renal dysfunction, and hypothyroidism (bexarotene)

### Interactions

- Oral retinoids are lipophilic → **fatty meals** ↑**bioavailability**
- Avoid vitamin A supplements (hypervitaminosis A)
- Methotrexate (MTX) (increased liver toxicity)
- **Alcohol + acitretin** → conversion of acitretin to etretinate, **hepatotoxicity**
- **Isotretinoin + tetracyclines** → **pseudotumor cerebri**
- **Bexarotene + gemfibrozil** → bexarotene is metabolized by cytochrome P450 3A4; avoid with gemfibrozil as it inhibits 3A4 → ↑plasma levels of bexarotene → **severe hypertriglyceridemia**
  - Treatment of ↑**LDL**: **statin** (may use any except simvastatin, because it interacts with 3A4)
  - Treatment of ↑**TG**: **fenofibrate** and/or omega 3

**Table 2-2.** Systemic Retinoids

Retinoid	Generation	Half-life	Metabolism	Excretion	Pregnancy Category	Nuclear Receptor Profile	Uses/Treatment*	Side Effects†	Miscellaneous
Tretinoin (ATRA or all- <i>trans</i> -RA)	First (nonaromatic)	1 hour	Hepatic	Bile, urine	X	All RAR	Acute promyelocytic leukemia		Treats APML (acute promyelocytic leukemia)
Isotretinoin (13- <i>cis</i> -RA)	First	<b>20 hours</b>	Hepatic, metabolizes to tretinoin	Bile, urine	X (women must have 2 negative pregnancy tests prior to initiating; requires contraception for 1 month before, during, and 1 month after cessation of therapy)	None	Severe acne and other follicular disorders Usual daily dose: 0.5–2 mg/kg per day Goal cumulative dose: <b>120–150 mg/kg</b> for severe acne	May flare in first few weeks; lag period of 1–3 months before effect, continued healing after discontinuation; 1/3 require second course <b>Hyperostosis</b> (long-term use), <b>pyogenic granulomas</b> , excessive granulation response, telogen effluvium, and <b>↑S. aureus infections</b>	<b>Only retinoid to affect sebum production so <i>P. acnes</i> unable to thrive</b> <b>Avoid with tetracyclines (↑risk of pseudotumor cerebri)</b>
Etretinate	Second (mono-aromatic)	<b>120 days</b>	Hepatic, metabolizes to acitretin	Bile, urine	No longer available	None	No longer available		<b>50 times more lipophilic than acitretin</b> → persists very long
Acitretin	Second	<b>2 days</b>	Hepatic, reesterification to etretinate by alcohol	Bile, urine	X (requires contraception for 1 month before, during, and <b>3 years</b> after cessation of therapy)	None	Psoriasis (pustular, erythrodermic, severe and recalcitrant plaque) Can be combined with PUVA (Re-PUVA); acitretin is given 10–14 days prior to starting PUVA, which accelerates the response Usual dose: 25–50 mg/day		<b>Must avoid concurrent alcohol use</b> because alcohol → conversion to etretinate → significantly prolonged effects
Bexarotene	Third (polyaromatic)	7–9 hours	Hepatic	Hepato-biliary	X (requires contraception for 1 month before, during, and 1 month after cessation of therapy)	All RXR	<b>CTCL</b> resistant to at least one systemic therapy Usual starting dose is 75 mg/day up to 300 mg/day Response to treatment takes up to 6 months	<b>Central hypothyroidism</b> (↑↑TGs (severe) Leukopenia)	<b>Avoid gemfibrozil</b> (worsens hyper-TG) “beXarotene = RXR”

\*Other off-label uses include: disorders of keratinization (ichthyosis, **pityriasis rubra pilaris**, **chemoprophylaxis** of premalignant and malignant skin cancers (nevroid basal cell carcinoma syndrome, xeroderma pigmentosum, and **transplant patients**).

†See side effects of systemic retinoids above for details.

## 2.3 CORTICOSTEROIDS (CS)

### Pharmacology key points (Table 2-3)

- Basic structure = 3 hexane rings and 1 pentane ring – modifications to this structure result in various CS (e.g., addition of 1,2 double bond to hydrocortisone → prednisone)
- **Exogenous CS absorbed in upper jejunum** – of note, more than 50% of prednisone is absorbed
- CS used in dermatology achieve their **desired effects via glucocorticoid activity**; **mineralocorticoid effects are never desirable** (sodium and water retention, HTN) for dermatologic purposes
  - Short-acting (hydrocortisone and cortisone):  
↓glucocorticoid, ↑mineralocorticoid activity
  - Intermediate-acting (prednisone, prednisolone, methylprednisolone, and triamcinolone):  
↑glucocorticoid and ↓mineralocorticoid activity
  - Long-acting (dexamethasone and betamethasone):  
↑↑glucocorticoid, no mineralocorticoid activity
- Glucocorticoid receptor (GCR) binds to CS in the **cytoplasm** → **translocates to nucleus** → binds nuclear DNA to act as transcription factor → altered gene regulation/transcription
- Cortisol-binding globulin (CBG) is main carrier protein – steroid that is bound to CBG is inactive and unbound steroid (free fraction) is active
  - ↑CBG: estrogen therapy, pregnancy, and hyperthyroidism → ↓CS free fraction
  - ↓CBG: hypothyroidism, liver disease, renal disease, and obesity → ↑CS free fraction
- **11β-hydroxysteroid dehydrogenase** in liver converts steroids to active forms:
  - Cortisone (inactive form) → cortisol (aka hydrocortisone, active form)
  - Prednisone (inactive form) → prednisolone (active form)
  - **Liver disease can impair conversion** → preferable to give active forms of steroids in this setting (prednisolone instead of prednisone, for example)

- MoA via immunosuppressive and antiinflammatory effects, primarily via cytokine alterations (e.g., ↓proinflammatory cytokines and ↑antiinflammatory cytokines)
  - **Decreased:** NFκB, AP-1, phospholipase A2, eicosanoids (e.g., leukotrienes, prostaglandins, 12-HETE, and 15-HETE), COX-2, activity of all types of WBCs, fibroblast activity, and prostaglandin production
  - **Increased:** IL-10 (major downregulator of cell-mediated immunity), antiinflammatory proteins (e.g., vasocortin, lipocortins, and vasoregulin), and ↑apoptosis of lymphocytes and eosinophils
  - Major effects on **cellular immunity** (> humoral immunity) and cell trafficking
- Physiologic CS therapy = 5 to 7.5 mg/day of prednisone; pharmacologic CS therapy is anything higher

### Adverse effects (systemic)

#### HPA axis suppression (see Box 2-1)

- Resulting from **systemic steroids** >>> topical CS (risk nearly nonexistent, except in setting of whole-body clobetasol application for autoimmune blistering diseases)
- Basics: hypothalamus releases corticotropin releasing factor (CRH) → anterior pituitary releases **ACTH** → adrenal glands release **cortisol**

#### Box 2-1. Layman's Explanation of Exogenous Adrenal Insufficiency

If you keep giving a person systemic steroids with glucocorticoid (cortisol-like) effects, their adrenal glands become "lazy" and stop making endogenous cortisol → over time, the adrenals become shrunken/atrophic, and can no longer produce adequate cortisol; immediately upon cessation of systemic steroid administration → "exogenous adrenal insufficiency" as a result of insufficient cortisol → may appear to be steroid withdrawal syndrome (most common), or very rarely, adrenal (Addisonian\*) crisis.

*\*Of note, the mineralocorticoid axis (renin-angiotensin-aldosterone) is almost NEVER suppressed in "exogenous adrenal insufficiency" → almost never get true adrenal (Addisonian) crisis with hypotension, coma.*

Table 2-3. Pharmacology Key Concepts – Systemic Corticosteroids

Corticosteroid	Equivalent Dose (mg)	Glucocorticoid Potency*	Mineralocorticoid Potency	Plasma Half-life (min)	Biologic Half-life (hr)
<b>Short-acting</b>					
Cortisone	25	0.8	2+	30–90	8–12
Cortisol (hydrocortisone)	20	1	2+	60–120	8–12
<b>Intermediate-acting</b>					
Prednisone	5	4	1+	60	24–36
Prednisolone	5	4	1+	115–212	24–36
Methylprednisolone	4	5	0	180	24–36
Triamcinolone	4	5	0	78–188	24–36
<b>Long-acting</b>					
Dexamethasone	0.75	20–30	0	100–300	36–54
Betamethasone	0.6–0.75	20–30	0	100–300	36–54

\*Glucocorticoid potency is expressed in a relative scale without specific units of measure; this relative potency number is inversely related to the equivalent dose in the first column. (From Wolverton S. Comprehensive Dermatologic Drug Therapy, 3rd Ed. Elsevier. 2012)



- HPA axis (CRH → ACTH → cortisol) is **suppressed** by use of exogenous CS
  - Hypothalamus: first to be suppressed, but quickest to recover
  - Adrenals: last to be suppressed, but **slowest to recover**
- **Mineralocorticoid axis** (renin-angiotensin-aldosterone) is **NOT suppressed** by exogenous CS used in dermatology → true adrenal (Addisonian) crisis w/ severe hypotension and coma is extremely uncommon in secondary exogenous adrenal insufficiency, because of the preserved MC axis function
- Exogenous adrenal insufficiency (HPA axis suppression) typically seen in patients taking pharmacologic CS doses for **≥3 to 4 weeks**
- Risk factors:
  - **Abrupt cessation** of CS (always taper if CS course is >4 weeks)
  - **Major stressor** (surgery, trauma, or illness)
  - **Divided dosing** (BID or TID)
  - Daily dose given at any time other than the morning
- QOD (alternate day) dosing → ↓risk of nearly all major complications
  - ↓risk of: HPA axis suppression, growth suppression, HTN, opportunistic infections, and electrolyte disturbances
  - Does **not** lower risk of: **cataracts** or **osteoporosis**
- Two clinical presentations of exogenous adrenal insufficiency:
  - **Steroid withdrawal syndrome (SWS)**: most common presentation; presents with (p/w) arthralgias, myalgias, mood changes, headache, fatigue, and anorexia/nausea/vomiting; **no change in serum cortisol level**, but rather ↓available intracellular CS
  - Adrenal (Addisonian) crisis: extremely uncommon; life-threatening; p/w symptoms of SWS + hypotension, ↓↓↓cortisol levels

### Glucocorticoid effects

- Hyperglycemia and increased appetite/weight gain

### Mineralocorticoid effects (tend to occur with CS with high MC effect)

- As a result of “aldosterone-like” activity of some CS
- p/w HTN, CHF, weight gain, and hypokalemia

### Lipid effects

- Hypertriglyceridemia (may result in acute pancreatitis), cushingoid changes, menstrual irregularity, and lipodystrophy (**moon face**, **buffalo hump**, and central obesity)

### Pediatric effects

- Growth impairment (as a result of ↓growth hormone and IGF-1 production)
- ↓risk with QOD dosing

### Bone effects

- Osteoporosis: QOD dosing does **NOT** ↓risk; consider calcium + vitamin D and/or bisphosphonates, teriparatide, nasal calcitonin; **greatest reduction in bone mass occurs in first 6 months**; ↑fracture risk in

postmenopausal women; **greatest absolute loss of bone mass occurs in young men** (they have highest baseline bone mass)

- Osteonecrosis: usually at least 2 to 3 month courses; proximal femur most common
- Hypocalcemia

### Gastrointestinal effects

- Bowel perforation, peptic ulcer disease (mainly if total dose ≥1 g, H2 antagonists or proton pump inhibitors can help), fatty liver changes, esophageal reflux, and nausea/vomiting

### Ocular effects

- Cataracts (risk does **NOT** change with QOD dosing), glaucoma, infections, and refraction changes

### Psychiatric changes

- Psychosis, hypomania, insomnia, agitation, and depression

### Neurologic effects

- Pseudotumor cerebri, seizures, epidural lipomatosis, and peripheral neuropathy

### Opportunistic infections

- Tuberculosis reactivation, deep fungi, prolonged herpes virus infections, and *Pneumocystis jiroveci* pneumonia
- ↓risk with QOD dosing

### Muscular effects

- Myopathy (proximal lower extremity weakness) and muscular atrophy

### Cutaneous effects

- ↓wound healing, striae, atrophy, telangiectasias, steroid acne, purpura, infections (staphylococcal, herpes virus), telogen effluvium, hirsutism, pustular psoriasis flare (upon drug withdrawal), perioral dermatitis, contact dermatitis, and hypopigmentation

## Contraindications

Systemic fungal infections, herpes simplex keratitis, and hypersensitivity reactions

## Pregnancy

Category C, but **likely safe for short courses** if needed (severe PUPPP or gestational pemphigoid, for example)

## Clinical use

Systemic steroids are used in autoimmune bullous dermatoses, connective tissue disorders (treatment of choice in dermatomyositis), vasculitides, neutrophilic dermatoses, allergic contact dermatitis, papulosquamous dermatoses, and various other dermatoses

- Pemphigus: start at 1 mg/kg daily in divided doses and increase up to 2 mg/kg daily (if needed) for 4 to 6 weeks, consolidate dose to once a day and taper quickly to 40 mg daily, and slowly thereafter; a steroid-sparing

agent should either be started at the get-go or before tapering

- Toxicodendron dermatitis: be careful not to stop oral CS too early because of the ↑likelihood of flare; best option is a 3 week tapering course starting at about 1 mg/kg daily
- Note that oral CS ↓acute pain in herpes zoster, but likely do not prevent postherpetic neuralgia
- Longer duration of treatment = ↑SE risk
- Divided dose regimens are more effective, but have a higher risk of SEs than single dose regimens (best taken in AM to simulate body's diurnal variation of cortisol production)
- Alternate day (QOD) dosing: the antiinflammatory effects of CS last longer than the HPA axis suppressive effects → QOD dosing helps maintain control of disease activity after course with daily CS

### Intramuscular CS

- Unique adverse effects: cold abscesses, subcutaneous fat atrophy, crystal deposition, menstrual irregularities, and purpura
- Main advantages (vs oral CS): compliance, can be given in setting of nausea/vomiting
- Main disadvantages (vs oral CS): ↑HPA axis suppression because levels are constant throughout the day (↑frequency of IM injections → ↑risk of HPA axis suppression), and less ability to precisely taper
  - Per Wolverton, do not use long-acting IM CS (such as Kenalog) more than 3 to 4×/year

### Pulse IV CS

- Generally 0.5–1 g of methylprednisolone IV over ≥ 1 h × 5 consecutive days
- Indications: systemic vasculitis, systemic lupus erythematosus, pyoderma gangrenosum, and bullous pemphigoid
- Adverse effects: sudden cardiac death, atrial fibrillation, anaphylaxis, electrolyte shifts, and seizures

### Intralesional CS

- Typically triamcinolone acetonide 2 to 40 mg/mL, depending on disorder/location/thickness of lesion
- Used for localized dermatoses such as prurigo nodularis, keloids, and alopecia areata
- SEs: atrophy (inject in dermis!) and hypopigmentation

### Topical CS

- Most commonly used in dermatology for various conditions including dermatitis and psoriasis
- Of note, more potent topical steroids (e.g., clobetasol) and those in more highly absorbed bases (e.g., gels and ointments) are more likely to → adverse cutaneous effects
  - Remember that topical steroids do not usually cause systemic symptoms!

### Monitoring

Consider monitoring:

- Fasting glucose levels, blood pressure (mild ↑ is ok), triglycerides, weight, height/weight for children, DEXA

scans (T score < -2.5 = osteoporosis), MRI if pain in hip/shoulder/knee (osteonecrosis), and slit-lamp examination q6–12 months

- TB screening and chest X-ray
- Tests to evaluate adrenal insufficiency
  - AM cortisol: primary screening tool, >10 mcg/dL = good basal adrenal function
  - 24 hour urine free cortisol: more accurate test for basal adrenal function (advantage); main disadvantage is patient compliance with 24 hour urine collection
  - ACTH stimulation: most commonly used provocative test for adrenal function; check basal cortisol level → then inject ACTH → check cortisol levels at 30 and 60 minutes
  - Others: insulin hypoglycemia, metyrapone, and corticotropin-releasing factor

## 2.4 IMMUNOMODULATORY AGENTS

### Apremilast

- Phosphodiesterase-4 (PDE-4) inhibitor
- Used for psoriasis and psoriatic arthritis
- Most common SEs are diarrhea and nausea – resolve on their own within 4 weeks usually
- Depression and weight loss have also been reported
- Dose halved in patients with severe renal impairment
- No laboratory monitoring required

### Janus kinase inhibitors

#### Tofacitinib

- JAK 1 and 3 inhibitor
- FDA approved for moderate to severe rheumatoid arthritis (RA) patients who have failed MTX
- Topical and oral have been tested in psoriasis; reports of oral used in alopecia areata
- Most common SEs: URI, mild headaches, and nausea
- May have ↓hemoglobin and mean neutrophil count, but usually normalize on treatment
- May have ↑LDL, HDL, CK, TGs, and LFTs
- Tuberculosis reactivation not reported

#### Ruxolitinib

- JAK 1 and 2 inhibitor
- FDA approved for treatment of intermediate- or high-risk myelofibrosis
- Topical version tested in psoriasis; reports of oral used in alopecia areata
- Mainly local SEs

### Azathioprine

#### Mechanism of action

- Azathioprine's active metabolite, 6-TG (thioguanine), is produced by the hypoxanthine guanine phosphoribosyltransferase (HGPRT) pathway and shares similarities with endogenous purines → therefore, it gets

incorporated into DNA and RNA → **inhibits purine metabolism and cell division** (particularly in fast-growing cells that do not have a salvage pathway, like lymphocytes) **Stop cell cycle S phase**

- **Xanthine oxidase and thiopurine methyltransferase (TPMT)** convert azathioprine into inactive metabolites
- **Diminishes T-cell function and antibody production by B-cells**

### Important pharmacology points

- TPMT activity is reduced in certain populations, and functional enzyme allele sequencing is available
  - **↓ activity of TPMT** (measured by allele activity) or **↓ xanthine oxidase** (as a result of **allopurinol** or **febuxostat**) → **↑ azathioprine levels** → **↑ risk of life-threatening myelosuppression**
  - **ACE inhibitors, sulfasalazine**, and concomitant use of **folate antagonists** also increases risk of myelosuppression
- Azathioprine may **decrease anticoagulant effects of warfarin** and reverse neuromuscular blockade

### Indications

- FDA approved indications: organ transplantation and severe RA
- Off-label dermatologic uses include **atopic dermatitis, chronic actinic dermatitis, Behçet's disease, bullous pemphigoid, cicatricial pemphigoid, dermatomyositis, oral lichen planus, and pemphigus**

### Side effects

- **Leukopenia, thrombocytopenia, and immunosuppression** (correlates with low TPMT activity)
- **Squamous cell carcinoma (SCC) and lymphoma** (particularly **non-Hodgkin's B-cell lymphoma**)
  - No clear evidence of increased risk for dermatologically dosed indications
- Infection (particularly **human papilloma virus, herpes simplex, and scabies**)
- **Teratogenicity**
- **Hypersensitivity syndrome** (usually between first and fourth week of therapy and more common in patients who are receiving concomitant cyclosporine or MTX)
- **Gastrointestinal SEs** – **most common** adverse effect of azathioprine – include nausea, vomiting, and diarrhea (often present between first and tenth day of therapy); also gastritis and pancreatitis
- **Transaminase elevation and severe hepatocellular toxicity** are rare

### Important monitoring points

- Baseline pregnancy test (for women of childbearing potential; **pregnancy category D**) and **tuberculin skin test** (strongly consider performing depending on clinical situation)
- Annual complete physical examination with particular attention to possible lymphoma and squamous cell carcinoma
- **CBC with differential and liver function tests every 2 weeks for the first 2 months and every 2 to 3 months thereafter**

### Interesting facts for boards

- The **killed hepatitis B virus** vaccine administered to patients on **azathioprine and corticosteroids** has shown a **decreased response**
- If given with **TNF- $\alpha$  inhibitor** → **↑ risk of hepatosplenic T-cell lymphoma**

## Cyclosporine

### Mechanism of action

- Forms a complex with cyclophilin, which inhibits calcineurin – an intracellular enzyme – which in turn reduces the activity of NFAT-1 (transcribes various cytokines, such as IL-2)
- **↓ IL-2 production** leads to **decreased** numbers of **CD4** and **CD8** cells.

### Important pharmacology points

- Cyclosporine should ideally be **gradually tapered** while an alternative therapy is instituted to prevent flaring
- **Maximum dermatologic dose = 5 mg/kg daily** and can be used continuously for up **to 1 year** according to the FDA (2 years for worldwide consensus data)
  - Cyclosporine **lipid nanoparticles formulation** **maximum dermatolyte dose = 4 mg/kg**
- For obese patients, ideal body weight should be used to calculate starting dose

### Indications

- **FDA approved for psoriasis**
- Off-label uses include **atopic dermatitis, chronic idiopathic urticaria, pyoderma gangrenosum, lichen planus, bullous dermatoses, autoimmune connective tissue diseases, neutrophilic dermatoses, and pityriasis rubra pilaris** among others

### SEs

- **Contraindicated** in patients with **cutaneous lymphoma** (risk of progression)
- **Nephrotoxicity** and **hypertension** are the two most notable SEs of cyclosporine, which are **dose- and duration-dependent**
  - Irreversible kidney damage is avoided if patients receive **dermatologic doses** (2.5–5 mg/kg daily), have **dose adjusted when creatinine increases by 30%** from baseline, and use cyclosporine for **no longer than 1 year**
  - **Hypertension** occurs in 27% of psoriasis patients who receive cyclosporine and is thought to be secondary to renal vasoconstriction
    - When HTN develops, it can be controlled with medication and is not a contraindication to continuing therapy
    - **Prescription of choice** = **CCBs** (e.g., nifedipine or isradipine), because they do not alter cyclosporine serum levels
- **↑ risk of NMSC** in psoriasis patients, particularly when treated >2 years
  - Risk of other malignancies, such as lymphoma, is unclear
- **Hyperlipidemia** not uncommon – dietary changes and ↑ physical activity should be recommended



- Other SEs include: **hypertrichosis, gingival hyperplasia, myalgia, paresthesia, tremors, malaise, hyperuricemia** (can precipitate gout), **hypomagnesemia, and hyperkalemia**

### Important monitoring points

- Recheck creatinine level if  $\uparrow$  by  $>30\%$  from baseline  $\rightarrow$  if remains elevated above  $30\%$ ,  $\downarrow$ dose by at least  $1 \text{ mg/kg}$  for 4 weeks, then:
  - If the creatinine level drops back down to  $<30\%$  above baseline, can continue therapy
  - If it does not drop, then discontinue therapy; if it returns to within  $10\%$  of baseline, cyclosporine can be resumed at lower dose
- If at any time creatinine increases by  $\geq 50\%$  above baseline, discontinue therapy until level returns to baseline
- Obtain two baseline blood pressures at least 1 day apart and two baseline creatinine values at least 1 day apart
- Baseline, BUN, CBC, LFTs, fasting lipid profile, magnesium, potassium, and uric acid
- Reevaluation of labs and blood pressure every 2 weeks for the first 1 to 2 months, then every 4 to 6 weeks with blood pressure checked at every visit

### Interesting facts for boards

- Recent case report suggesting efficacy in treating poststreptococcal pustulosis and SPTCL as single agent therapy

## Methotrexate

### Mechanism of action

- Binds dihydrofolate reductase with greater affinity than folic acid  $\rightarrow$  **prevents conversion of dihydrofolate to tetrahydrofolate** (a necessary cofactor of purine synthesis)  $\rightarrow$  inhibition of cell division

### Important pharmacology points

- The inhibition of dihydrofolate reductase may be bypassed by **leucovorin (folinic acid)** or **thymidine**
  - Folinic acid is an active, naturally occurring version of folate (**vitamin B<sub>9</sub>**); most commonly used medication for rescue of high-dose MTX adverse effects/overdose
- **Folic acid (synthetic) and folinic acid (naturally occurring):  $\downarrow$ MTX-induced adverse effects**
  - $\downarrow$ GI adverse effects by  $26\%$  (nausea, vomiting, and abdominal pain)
  - $\downarrow$ risk of LFT abnormalities by  $76\%$
  - $\downarrow$ risk of pancytopenia
  - $\uparrow$ ability to tolerate MTX ( $\downarrow$ MTX discontinuation rate for any reason)
- Recent Cochrane review showed that coadministration of **folates (folic acid or folinic acid) does NOT decrease efficacy of MTX**
- MTX-induced hepatic fibrosis:
  - Testing indicated for high cumulative doses ( $\geq 1.5\text{--}4 \text{ g}$ ), particularly for patients with preexisting liver disease, alcohol abuse, hepatitis C, psoriasis, or those who did not receive folic acid supplementation
  - **Liver biopsy (gold standard)**

- Other tests for which further studies are needed to confirm utility: ultrasound, dynamic radionuclide scans, and the amino terminus of type III procollagen peptide assay (PIIIP)
- Pretreatment liver biopsy may be considered for patients who have baseline  $\uparrow$ LFTs, history of liver disease, heritable liver disease, diabetes, obesity, or exposure to alcohol/hepatotoxic drugs

### Indications

- FDA approved for extensive, severe, debilitating, or recalcitrant psoriasis and Sezary syndrome
- Off-label dermatologic uses include: PLEVA, LyP, pemphigus, pemphigoid, autoimmune connective tissue diseases, sarcoidosis, mycosis fungoides, and cutaneous vasculitis

### SEs

- **Absolute contraindications:** pregnancy (category X) and lactation
- Relative contraindications: unreliable patient,  $\downarrow$ renal function, hepatic disease, metabolic disease (i.e., obesity or diabetes mellitus), severe hematologic abnormalities, man or woman contemplating conception (3 months off drug for men, off one ovulatory cycle for women), active infectious disease or history of potentially serious infection that could reactivate, and immunodeficiency syndrome
- Rarely reported to cause acute pneumonitis, which is idiosyncratic and can be life threatening if MTX is not stopped, and pulmonary fibrosis (even less common).
  - Routine radiography or pulmonary function studies, without symptoms to suggest pneumonitis, are not helpful in preventing lung toxicity.
- **Pancytopenia**, which can be life threatening, usually occurs **early** (initial 4–6 weeks) in therapy and may be idiosyncratic
  - Risk factors: old age, poor renal function, and lack of folic acid supplementation
- No data that patients with psoriasis and taking MTX have  $\uparrow$ risk of malignancy such as lymphoma
- **GI SEs are common** (nausea, anorexia  $>$  diarrhea, vomiting, and ulcerative stomatitis)
- MTX has been reported to accumulate in renal tubules and cause renal toxicity when given at high doses for chemotherapy
- Other adverse effects: alopecia, headaches, fatigue, dizziness, accelerated nodule development in patients with rheumatoid arthritis (similar to rheumatoid nodules, but smaller and classically on fingers) and **phototoxicity** (including **UV and radiation "recall reactions"**)
- $\uparrow$ risk **myelosuppression** when coadministered with agents that inhibit folic acid metabolism (e.g., **trimethoprim, sulfonamides, and dapsone**) or increase MTX levels by displacing plasma proteins (tetracyclines, phenytoin, phenothiazines, sulfonamides, NSAIDs, and salicylates)

### Important monitoring points

- CBC w/ differential, LFTs, creatinine, BUN, and viral hepatitis panel at baseline, then repeat weekly for first

month (excluding the viral hepatitis panel), and gradually decrease frequency to every 3 to 4 months (e.g., every 2 weeks  $\times$  2 months, every month  $\times$  2 months, every 3 months thereafter)

- Liver biopsy information discussed on p. 35
- “**Leucovorin rescue**”: folinic acid (leucovorin) bypasses dihydrofolate reductase  $\rightarrow$  may be given when MTX induces significant myelosuppression

### Interesting facts for boards

- Pediatric patients may have reduced oral absorption of MTX when taken with various foods or have underlying diseases and therefore may consider injectable form of MTX for this select population
- MTX causes **UV and radiation recall** (toxic cutaneous reactions reappear on previously irradiated skin)

## Mycophenolate mofetil

### Mechanism of action

- Binds and inhibits **inosine monophosphate dehydrogenase** – a key enzyme for the *de novo* synthesis of purines – which is essential in activated lymphocytes

### Important pharmacology points

- Requires **gastric acidity** for cleavage into its active state (antacids and proton pump inhibitors  $\downarrow$  serum levels)
- Dermatologic doses range from 2 to 3 g divided in twice daily doses

### Indications

- FDA approved for renal, cardiac, and liver allograft rejection prevention
- Off-label dermatologic uses include: psoriasis, atopic dermatitis, pemphigus, pemphigoid, autoimmune connective tissue diseases, vasculitis, lichen planus, and sarcoidosis

### Side effects

- Absolute contraindications: pregnancy (category D) and drug allergy
- Relative contraindications include lactation (may be excreted in breast milk), peptic ulcer disease, hepatic or renal disease (may require dose adjustment), drugs that interfere with enterohepatic circulation (e.g., cholestyramine), and concomitant administration with azathioprine ( $\uparrow$  risk of bone marrow toxicity)
- **Risk of carcinogenesis** (lymphoma and lymphoproliferative malignancies) shown in transplant population (who usually had several immunosuppressive medications given concomitantly) – unknown whether this holds true in dermatologic patients and whether there is increased risk of nonmelanoma skin cancer
- **Most common SEs = diarrhea, abdominal pain, nausea, and vomiting**
- Associated with a form of neutrophil dysplasia termed pseudo-Pelger-Huet anomaly, which is characterized by nuclear hypolobulation with a left shift – this may predict the development of neutropenia

### Monitoring guidelines

- CBC with differential, basic metabolic profile (with creatinine) and LFTs at baseline, then 2 to 4 weeks after initiating treatment or dose escalation, and then every 2 to 3 months once dose is stable
- Baseline hepatitis B and C panel, tuberculosis screen, and pregnancy test

## Cytotoxic agents

### Hydroxyurea

- Impairs DNA synthesis through inhibition of ribonucleotide diphosphate reductase; hypomethylates DNA resulting in altered gene expression
- FDA approved for sickle cell anemia, chronic myelogenous leukemia, SCC of head and neck, and some forms of metastatic melanoma
- Dermatologic uses are mainly off-label for treatment of recalcitrant psoriasis, Sweet’s syndrome, erythromelalgia, and hypereosinophilic syndrome
- Severe anemia, thrombocytopenia, and leukopenia are relative contraindications
- **Most common adverse effect: megaloblastic anemia** (myelosuppression)
- Can cause **dermatomyositis-like eruption**, lichenoid drug eruption resembling graft-versus-host disease, **leg ulcers**, alopecia, photosensitivity, radiation recall, and **hyperpigmentation of the skin and nails**

### Cyclophosphamide

- An **alkylating agent** (exerts its effect by directly damaging DNA via cross-linking)
  - Nitrogen mustard derivative
  - Aldophosphamide – one of its metabolites – is cleaved intracellularly into acrolein and enhances cellular damage by depleting glutathione store
- FDA approved for the treatment of mycosis fungoides (advanced disease)
- Off-label dermatologic uses: severe immunobullous disease (e.g., ocular cicatricial pemphigoid), severe systemic vasculitides, neutrophilic dermatoses, and autoimmune connective tissue diseases
- **Hemorrhagic cystitis** occurs in 5% to 41% as a result of acrolein (prevented by adequate hydration as well as mesna, which binds acrolein in the bladder and reduces irritation)
  - a/w  $\uparrow$  **risk of transitional cell carcinoma** of the bladder, non-Hodgkin’s lymphoma, leukemia, and squamous cell carcinoma (in transplant and oncology patients)
  - Monitoring: periodic urine analysis with cytologic examination
- Nausea and vomiting are the most common SEs and can be decreased by coadministering with ondansetron and dexamethasone
- $\uparrow$  **risk infertility**: amenorrhea (27%–60%); premature ovarian failure (up to 80%)
- Cutaneous SEs permanent pigmented band on the teeth, **anagen effluvium**, and **hyperpigmentation of skin and nails**

## Chlorambucil

- Alkylating agent that directly damages DNA via cross-linking
- FDA approved for chronic lymphocytic leukemia
- Off-label dermatologic uses: NXG (shown to be effective and safe in a retrospective review of 48 cases), pyoderma gangrenosum, and several immunobullous and connective tissue diseases, such as Behcet's and dermatomyositis
- Allergy to nitrogen mustard is a contraindication
- Epileptogenic and mood-altering potential
- Other SEs include nausea, vomiting, azoospermia, amenorrhea, pulmonary fibrosis, hepatotoxicity, bone marrow suppression, and oral ulcers

## Antimalarial agents

- Include hydroxychloroquine (HCQ), chloroquine (CQ), and quinacrine (taken off the market in the United States, but still available in compounding pharmacies)

### Mechanism of action

- Antimalarials work via several different proposed mechanisms:
  - **Inhibit ultraviolet-induced cutaneous reactions** by binding to DNA and inhibiting superoxide production
  - Raise intracytoplasmic pH and stabilize the microsomal membrane → ↓ability of macrophages to express MHC complex antigens on cell surface
  - Reduce lysosomal size and impair chemotaxis
  - Inhibit platelet aggregation and adhesion

### Important pharmacology points

- CQ and HCQ have long half-lives and steady-state concentration is attained at 3 to 4 months, which explains the long treatment duration required to achieve clinical benefit

### Indications

- FDA approved for SLE, malaria, and RA
- Off-label dermatologic uses: particularly useful in **disorders with significant lymphocytic infiltrates** (polymorphous light eruptions, lymphocytic infiltrate of Jessner, lupus panniculitis, and discoid LE)

### Side effects

- Pregnancy category C
- Absolute contraindications include hypersensitivity to the drug (may have cross-reaction between CQ and HCQ); continued use is contraindicated in patients who develop **retinopathy**
- Relative contraindications include severe blood dyscrasias, significant hepatic dysfunction, significant neurologic disorders, retinal or visual field changes, pregnancy and lactation (however, some suggest that the risk of discontinuing treatment in pregnancy in patients with SLE outweighs the risk of toxicity to the fetus), and psoriasis

- CQ is contraindicated in patients who have myasthenia gravis
- **Mucocutaneous drug reactions:**
  - Yellow pigmentation of the skin (quinacrine)
  - Drug-induced LP
  - Morbilliform hypersensitivity eruption; may also present as erythroderma or SJS
    - **Risk is much greater in dermatomyositis (31%) than lupus (3%)**
  - Psoriasis exacerbation (CQ in particular)
  - **Bluish-gray to black hyperpigmentation** in 10% to 30% of patients treated for ≥4 months typically affecting the **shins** (clinically indistinguishable from type II minocycline hyperpigmentation), face, and palate
  - **Nail hyperpigmentation**
- Ophthalmologic toxicity includes corneal deposits (keratopathy), neuromuscular eye toxicity (ciliary body dysfunction), and retinopathy (maculopathy)
  - All except retinopathy are reversible with discontinuation of treatment
  - **Ocular toxicity is NOT seen in quinacrine therapy**
- Current eye monitoring recommendations (based on recent ophthalmologic literature):
  - Baseline examination including visual field testing
  - Dilated examination and visual acuity testing **within first year** of starting therapy
  - Dilated examination and visual acuity testing **yearly after 5 years** of treatment (some patients, such as the elderly, may require more frequent examinations)
- GI SEs (CQ > HCQ): most common reason for early reduction or D/C of treatment
- Restlessness, excitement, confusion, and seizures (usually in patients on higher than recommended doses)
- Rare, but potentially fatal, bone marrow toxicity has been reported with quinacrine and agranulocytosis with CQ
- **Hemolysis in the G6PD deficient population** is mainly a concern for 8-aminoquinoline and primaquine, but not for usual doses of HCQ and CQ

### Important monitoring points

- G6PD testing is not necessary for HCQ, CQ, and quinacrine given low risk of hemolysis with therapeutic doses
- Baseline ocular examination as mentioned on [p. 37](#); CBC w/ differential, complete metabolic profile, and LFTs periodically; G6PD screening and measurement of porphyrin levels in selected clinical settings

### Interesting facts for boards

- The use of HCQ delays the time to fulfill criteria for SLE in patients treated for cutaneous LE
- Low-dose HCQ or CQ may be used in porphyria cutanea tarda (i.e., 100–200 mg/day of HCQ vs 400 mg/day used for DLE)
- **Quinacrine may be added to HCQ or CQ for ↑therapeutic effect**
- CQ and HCQ should **not** be given together

## Dapsone

### Mechanism of action

- Inhibits myeloperoxidase → ↓oxidative damage to normal tissue in various **neutrophilic dermatoses** (affects eosinophils and monocytes to a lesser extent)
- Also ↓hydrogen peroxide and hydroxyl radical levels
- It may also ↓chemotaxis of neutrophils, although this has not been demonstrated in therapeutic doses

### Important pharmacology points

- Dapsone undergoes significant enterohepatic recirculation, thus remaining in the circulation 30 days after a single dose
- Hemolysis has been demonstrated in nursing infants of mothers taking dapsone. No harmful *in utero* developmental effects are demonstrated when taken during pregnancy; however, it is classified as pregnancy category C
- There is significant variability both in individual rates of acetylation (not clinically relevant) and hydroxylation. The hydroxylamine metabolite (DDS-NOH) is responsible for hematologic adverse effects.

### Indications

- FDA approved indications are **dermatitis herpetiformis** and leprosy
- Off-label dermatologic uses are numerous and include various **neutrophilic dermatoses** (linear IgA dermatosis, bullous SLE, erythema elevatum diutinum, pyoderma gangrenosum, Sweet's syndrome, neutrophilic urticaria, subcorneal pustular dermatosis/IgA pemphigus and Behcet's syndrome), and vasculitides

### Side effects

- Cross-reactivity between dapsone and sulfapyridine, or other sulfonamide-type drugs, is quite rare
- Greater care should be taken in patients with increased risk of developing hematologic, cardiovascular, or pulmonary adverse effects (patients with **G6PD deficiency**; significant cardiopulmonary, liver, or renal disease)
- Patients with preexisting peripheral neuropathy should be treated with caution
- **Hemolytic anemia** and **methemoglobinemia**: dose-related and occurs in **ALL** individuals to some degree (related to oxidative stress from N-hydroxy metabolites)
  - ↑methemoglobin → ↓oxygen-carrying capacity → may exacerbate preexisting cardiopulmonary disease
- **Agranulocytosis**, the most serious **idiosyncratic** reaction to dapsone, usually occurs at 7 weeks (3–12 weeks) and may manifest as fever, pharyngitis, and occasionally sepsis
  - Most recover quickly after cessation of dapsone; may consider giving G-CSF
- **Peripheral neuropathy** (predominantly **distal motor**) + some degree of sensory involvement; may present as wasting of hand muscles; reversible if detected early
- Nausea, gastritis, reversible cholestasis and hepatitis, and hypersensitivity syndrome (typically after 3–12 weeks of therapy) have also been reported

### Important monitoring points

- **Baseline G6PD level** (lower levels may preclude patient from receiving medication, or require ↓dose)
- CBC w/ differential, LFTs, renal function tests, and UA at baseline
- Must monitor CBC very closely during “high-risk window” for agranulocytosis: **CBC weekly for 4 weeks, then every 2 weeks until 3 months into treatment** (agranulocytosis is most common in first 12 weeks of treatment)
- After 3 months, continue checking renal function, LFTs, and UA every 3 to 4 months
- Methemoglobin levels are needed if there is clinical suspicion of decreased oxygen circulation or anemia

### Interesting facts for boards

- Cimetidine decreases risk of methemoglobinemia without affecting dapsone's plasma level
  - Vitamin E may also provide small amount of protection against methemoglobinemia
- Methemoglobinemia emergency → use **methylene blue**
- Worsening of methemoglobinemia has been shown intra- and postoperatively after both local amide and general anesthetic; vitamin C can be used when this occurs
- Most patients treated with dapsone for **dermatitis herpetiformis rapidly respond within 24 to 36 hours**; bullous SLE also responds very well to Dapsone (in contrast with EBA, which does not)

## Biologics

### TNF- $\alpha$ inhibitors

#### Etanercept

- Fully human dimeric **fusion** protein (TNF-receptor linked to Fc portion of IgG) that binds both TNF- $\alpha$  (soluble and membrane-bound) and TNF- $\beta$
- Subcutaneous

#### Infliximab

- **Chimeric** monoclonal IgG antibody binding TNF- $\alpha$  only (targets soluble and transmembrane TNF-receptor)
- Intravenous

#### Adalimumab

- **Fully human** monoclonal IgG antibody against transmembrane TNF-receptor
- Subcutaneous

### Indications

- FDA approved for plaque psoriasis and psoriatic arthritis. Off-label dermatologic uses include neutrophilic dermatoses, autoimmune connective tissue diseases, granulomatous dermatoses, bullous dermatoses, hidradenitis suppurativa, and pityriasis rubra pilaris.

### Side effects

- Pregnancy category B
- Contraindicated if patient has active infection



- **Injection site reactions: etanercept (14%) > adalimumab (3.2%)**
  - For etanercept, these are believed to be most pronounced during the second injection and usually improve after 1 month of therapy (hypothesized to be caused by delayed-type hypersensitivity)
- **Infliximab commonly causes infusion reactions (20%):**
  - p/w nausea, headache, flushing, dyspnea, injection site infiltration, and taste perversion
  - **↓infusion rate and premedication** may help
  - Epinephrine and systemic corticosteroids are given for serious reactions (less than 1% of treated patients) including hypotension, chest pain, dyspnea, anaphylaxis, and convulsions
- **Infliximab-associated-antidrug antibodies (ADA) → ↑infusion reactions and ↓efficacy**
- Practice caution if there is family history of **demyelinating disease** – multiple case series report patients on TNF-inhibitors developing various demyelinating diseases (e.g., MS, Guillain-Barré syndrome, and optic neuritis)
- **Psoriasis, palmoplantar pustulosis, and cutaneous vasculitis have been reported with all TNF-inhibitors**
- Malignancy risk, particularly **lymphoma** and possibly skin cancer, may be increased in patients treated with biologic agents
  - Hepatosplenic T-cell lymphoma (fatal) may be seen in patients on TNF-inhibitor + azathioprine
- ↑risk of tuberculosis (primary infection and reactivation), invasive fungal infections, and opportunistic infections like legionella and listeria reported with all TNF-inhibitors
- Conflicting evidence exists as to whether TNF-inhibitors may increase risk of developing or exacerbating **congestive heart failure** → should be used w/ caution in at-risk population (**particularly infliximab**)
- Although there are relatively high rates of ANA and anti-dsDNA positivity in patients treated with biologic agents (infliximab in particular), SLE or lupus-like syndrome is uncommon and resolves after drug discontinuation

### Important monitoring points

- Although there are no strict FDA mandated guidelines, most authors agree with checking **PPD/quantiferon gold annually, viral hepatitis panel at baseline, and CBC w/ diff + LFTs every either 3 (for infliximab) or 6 to 12 months (for etanercept and adalimumab)** given rare hematologic toxicity and liver failure/autoimmune hepatitis (with ASMA autoantibodies).

### Interesting facts for boards

- **Can be used safely in patients with active hepatitis C infection.** Caution is advised, however, if patient has HBV because reactivation has been reported.
- Multiple case reports claim safety in HIV patient population
- ADA can either be neutralizing or nonneutralizing
  - **Neutralizing ADA** usually form before week 24 of treatment and interfere with the biologic agent's binding activity → **↓decrease efficacy**

- Studies show that ADA's directed against infliximab (5.4%–43.6%) and adalimumab (6%–45%) → **↓efficacy and serum levels**
  - Effect not seen with etanercept
  - In one study, the adalimumab dose interval was shortened because of lack of efficacy in 15 patients, 7 with and 8 without ADA. Improvement in responder status only occurred in 1 of 7 patients with ADA compared with 4 of 8 without ADA.
- **Coadministration with MTX may lead to lower rates of ADA**

### Ustekinumab

- **Fully human monoclonal IgG1** antibody directed against the common **p40 subunit** of IL-12 and IL-23
- FDA approved for adults with psoriasis and psoriatic arthritis; some evidence for efficacy in hidradenitis suppurativa
- Head-to-head trial with etanercept (50 mg biweekly) suggests superior efficacy of ustekinumab, at both 45 mg and 90 mg, given at week 0 and 4 when compared with week 12
- **Upper respiratory infections are the most frequently reported adverse effects;** also increased risk of infections, including TB reactivation, fungal disease, and viral illnesses
- Possible association with **reversible posterior leukoencephalopathy syndrome**, although more studies are needed
- No dose-related/cumulative toxicity was observed with increasing duration of ustekinumab exposure for up to 5 years
- Rates of adverse effects reported in ustekinumab psoriasis trials are generally comparable with those reported for other biologics approved for the treatment of moderate-to-severe psoriasis

### Rituximab

- **Chimeric IgG** monoclonal antibody targeting the B-cell surface antigen (**CD20**)
- FDA approved for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and RA unresponsive to other treatments
- Off-label dermatologic uses include bullous dermatoses (especially **pemphigus vulgaris** and **severe bullous pemphigoid**), autoimmune connective tissue diseases, chronic graft-versus-host disease, vasculitis, and cutaneous B-cell lymphoma
- Depletion of B-cells occurs within 2 to 3 weeks of initial treatment with sustained depletion for an average of 6 months; B-cell numbers return to normal within the first year of treatment
- Relative contraindication in patients with history of bronchospasm, hypotension, or angioedema
- Pregnancy category C
- Common adverse effects include: hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia, and pruritus; most common are **infusion**

reactions, which are generally mild and occur with the first infusion

- Patients with history of cardiac or pulmonary conditions should be more closely monitored as they are susceptible to severe infusion reactions
- Serious SEs: HBV reactivation, progressive multifocal leukoencephalopathy SJS/TEN, serious infection, hepatic failure and myelosuppression

### IL-1 inhibitors

- Canakinumab, Anakinra, Rilonacept, and Gevokizumab
- Anakinra is FDA approved for moderate to severe RA that has failed other disease modifying treatments
- Off-label uses in dermatology: pyoderma gangrenosum, PAPA syndrome, hidradenitis suppurativa, lamellar ichthyosis, Sweet's syndrome, panniculitis, Muckle-Wells syndrome and other autoinflammatory syndromes, and SAPHO syndrome
- Risk of tuberculosis reactivation appears to be lower in IL-1 inhibitors than in TNF- $\alpha$  agents, although more studies are needed
- Most common adverse effects are injection site reactions; important to monitor absolute neutrophil count as neutropenia can occur
- IL-1 inhibitors should not be initiated in patients with active infections; the safety of this agent in immunosuppressed patients or those with chronic infections has not been evaluated

### IL-17 inhibitors

- Ixekizumab and secukinumab neutralize IL-17A
- Brodalumab antagonizes the IL-17 receptor
- These agents have produced the most impressive results to date for treatment of plaque psoriasis
- Similar SE profile to TNF- $\alpha$  inhibitors but no increased risk of lymphoma, heart failure or neuromuscular disorders has been reported
- Most commonly reported SE = nasopharyngitis
  - Other common SEs include upper respiratory infection, injection site reactions, and headache; candidiasis and herpes infections have also been reported
- Long-term efficacy and safety in all three agents has been demonstrated in moderate to severe plaque psoriasis
- IL-17 inhibitor class shown to be more effective than etanercept and ustekinumab:
  - A 12-week trial demonstrated that 77.1% and 67.0% of patients treated with 300 mg and 150 mg of secukinumab every 4 weeks, respectively, achieved PASI 75 compared with only 44.0% with etanercept
  - Ixekizumab also superior to etanercept in comparative trials

### Omalizumab

- Monoclonal anti-IgE antibody  $\rightarrow$   $\downarrow$  IgE levels and  $\downarrow$  IgE receptors on mast cells and basophils
- FDA approved for allergic asthma and chronic idiopathic urticaria

- SEs: anaphylaxis, malignancy, and injection site reaction

## 2.5 ONCOLOGIC AGENTS IN DERMATOLOGY

### Vismodegib

- Targets sonic hedgehog pathway by inhibiting smoothened receptor  $\rightarrow$  GLI1/2 transcription factors stay inactive  $\rightarrow$  inhibition of transcription of target genes
- Used for metastatic and locally advanced basal cell carcinoma, as well as those unamenable to surgery/radiation; may be used in patients with nevoid basal cell carcinoma syndrome
- SEs: muscle spasms (#1), alopecia, dysgeusia, fatigue, nausea, anorexia, and diarrhea

### BRAF inhibitors (vemurafenib and dabrafenib)

- BRAF: serine/threonine signal transduction kinase important to the MAPK pathway, which regulates cell division
  - Mutations in BRAF can  $\rightarrow$  various malignancies
- BRAF inhibitors target the V600E mutation of BRAF
  - V600E = valine (V) is replaced by glutamic acid (E) at amino acid position number 600
- Used in late stage melanoma,  $\uparrow$  survival rates
- Cutaneous reactions are most common SE:
  - Exanthematous rash – papulopustular on face, torso, and arms
  - Keratotic lesions
    - SCC and keratoacanthoma
      - ◆ Treatment = excision/Mohs; dose modification NOT required
    - Verrucous keratosis: most common skin lesion; benign
  - Photosensitivity, alopecia, and plantar hyperkeratosis
- Noncutaneous SEs: arthralgias, nausea, diarrhea, fatigue, QT prolongation, and retinal vein thrombosis

### MEK inhibitors (trametinib)

- Inhibit MEK1/2 of the MAPK pathway
- Used in late stage melanoma
- Can be used as monotherapy or in combination with dabrafenib (combination more effective than BRAF inhibitor alone in BRAF V600E mutation-positive metastatic melanoma)
  - May  $\downarrow$  SCC risk when given with BRAF inhibitor
- Nonspecific cutaneous and noncutaneous reactions (GI SEs most common (diarrhea, nausea, and vomiting), hypoalbuminemia, dysgeusia, xerostomia, cardiomyopathy, interstitial lung disease, and retinal vein occlusion)



## Ipilimumab

- Fully human monoclonal antibody that binds and inhibits cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) → ↑ T-cell activation against tumor cells
- Used to treat metastatic melanoma
- SEs are called **immune-related adverse events**:
  - Cutaneous SEs are most common (24%)
    - Rash (most common)**: maculopapular or eczematous on trunk/extremities
    - Pruritus, alopecia, and hypopigmentation
  - Gastrointestinal SEs (most severe issue)
    - Most common: diarrhea, constipation, and bloating
    - Most severe: **life-threatening colitis** with bowel perforation
  - Less common: hypothyroidism, transaminitis, hepatitis, and hypopituitarism

## PD-1 inhibitors (pembrolizumab, nivolumab)

- Ipilimumab was the first checkpoint inhibitor to improve overall survival in randomized phase III trials of advanced melanoma; however, checkpoint inhibitors that target the Programmed cell death-1 (PD-1) receptor have quickly become the preferred approach to immunotherapy since they are **more effective** and have **fewer side effects**
- PD-1 is an immune checkpoint receptor expressed by activated T cells
  - Normally functions as a “brake” on the immune response
  - PD-1 on activated T cells binds to its ligands PD1-L1 (B7-H1) and PD1-L2 (B7-DC), which are expressed on tumor cells → deactivation of T cells → loss of immune response against tumor
- Nivolumab and pembrolizumab
  - Monoclonal antibodies that target PD-1** → prevent T cell deactivation → ↑ immune-mediated tumoricidal activity
  - Both are FDA approved for advanced melanoma
  - Phase 3 RCTs in patients w/advanced melanoma have demonstrated ↑ **overall survival**, ↑ **progression-free survival**, and **fewer side effects** with either agent when compared to ipilimumab or conventional chemotherapy
    - Some patients have **durable responses** even after completion of treatment
    - Efficacy improved when used in combination with ipilimumab (main disadvantage = ↑ immune-mediated side effects)
  - Most common adverse events: fatigue, pruritus, and rash
    - Less common (far less common than w/ ipilimumab): pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, and thyroid dysfunction

## Imatinib mesylate

- Tyrosine kinase inhibitor
  - Binds to the kinase domain of various tyrosine kinases (e.g., Bcr-Abl, c-Kit receptor [CD117], and platelet-derived growth factor receptor [PDGFR])
- Dermatologic applications: melanoma, myeloproliferative hypereosinophilic syndrome, and **dermatofibrosarcoma protuberans**
- Cutaneous reactions are common
  - Most common: superficial edema (**periorbital edema mainly**)
  - Second most common: **rash** (maculopapular, nonspecific)
  - Other SEs: **hypopigmentation/depigmentation** (via inhibition of c-Kit pathway, which is involved in melanocyte activation), hyperpigmentation (less common), lichenoid eruptions (oral and mucosal), and photosensitivity

## Mechlorethamine hydrochloride

- a nitrogen mustard alkylating agent, is used for patch/plaque MF; contact dermatitis is the most common SE, but anaphylaxis and SCC development are the most concerning
- Carmustine is also an alkylating agent used for patch/plaque MF; it can cause severe local reactions and myelosuppression

## Other topical agents for NMSC (see Table 2-4)

## 2.6 ANTIMICROBIAL AGENTS

### Topical antibacterial agents

#### Bacitracin

- Made by *Bacillus subtilis*
- Bactericidal
- Binds to C55-prenol pyrophosphatase → disruption of **bacterial cell wall** peptidoglycan synthesis
- Activity against *Neisseria* and gram positives (GP); poor activity vs gram negatives (GN)
- Commonly causes **allergic contact dermatitis** (especially common in patients with stasis dermatitis/ulcers)

#### Polymyxin B

- Made by *Bacillus polymyxa* and *B. subtilis*
- Bactericidal
- ↑ **cell membrane permeability** via **detergent-like phospholipid interaction**
- Activity against GN (e.g., *Pseudomonas*)
- Pregnancy category B

**Table 2-4.** Topical Treatments for Actinic Keratoses and Non-Melanoma Skin Cancer

	Mechanism of Action	FDA Approved Indications	Adverse Effects
5-fluorouracil	Antimetabolite/pyrimidine analog which binds to <b>thymidylate synthase</b> (normally converts deoxyuridine → thymidine), and results in ↓DNA synthesis	AKs, and superficial BCCs (5% strength only)	Local reactions (e.g., erythema, blistering, necrosis, erosions, and burning) Pregnancy category X
Imiquimod	Activator of <b>Toll-like receptors 7 and 8</b> → activation of NF-κB transcription factor → ↑ cytokines/chemokines (e.g., <b>TNF α and IFN γ</b> ) → innate/acquired immune pathway stimulation → antitumor and antiviral activity Also antiangiogenic, proapoptotic, and ↑ lymphatic transport of immune cells/factors → tumor destruction	AKs, superficial BCCs (5% strength only), and genital/perianal warts	Local reactions similar to 5-fluorouracil Sometimes <b>flu-like or GI symptoms</b> (especially if larger areas treated), and <b>psoriasis exacerbation</b> Pregnancy category C
Diclofenac	↓ cyclooxygenase enzymes → ↑apoptosis	AKs	Mild irritation, rare photosensitivity/photocontact dermatitis; avoid in patients with NSAID hypersensitivity and known bleeding diatheses Pregnancy category B
Ingenol mebutate	1) induces rapid cellular death (within hours) via mitochondrial swelling/plasma membrane disruption; 2) intense inflammatory response (within days) via protein kinase C activation	AKs	Local reactions (erythema, scaling, and crusting), which are worse on days 4–7

## Neomycin

- Aminoglycoside made by *Streptomyces fradiae*
- **Binds 30s subunit of bacterial ribosomal RNA** → ↓protein synthesis
- Activity against GP and GN
- Can be combined with bacitracin and polymyxin B (e.g., Neosporin)
- **Common contact allergen**, like bacitracin (**co-react w/ each other**); allergy more common in those w/ stasis dermatitis and when applied to ulcers; possibility of ototoxicity/nephrotoxicity but very rare
- Pregnancy category D

## Mupirocin

- Made by *Pseudomonas fluorescens*
- Binds to bacterial **isoleucyl tRNA synthetase** → ↓RNA/protein synthesis
- Activity against **MRSA** (can ↓nasal carriage) and *S. pyogenes*; resistance has been reported
- Not effective against *Pseudomonas* (made by *Pseudomonas*)
- Pregnancy category B

## Retapamulin

- Pleuromutilin made by *Clitopilus scyphoides*
- Binds to **L3 protein on 50s subunit of bacterial ribosome** → ↓protein synthesis
- Activity against **MRSA**, *S. pyogenes*, and anaerobes; FDA approved for impetigo to MSSA and *S. pyogenes*
- Can cause contact dermatitis

## Gentamicin

- Aminoglycoside made by *M. purpurea*

- Binds to bacterial 30s ribosomal subunit → ↓protein synthesis
- Activity against GP and GN (e.g., *Pseudomonas*)

## Silver sulfadiazene

- **Binds bacterial DNA** → ↓DNA synthesis; also disrupts cell walls and membranes
- Activity against GP and GN, including MRSA and *P. aeruginosa*
- May cross-react with sulfonamides; pregnancy category B
- Used extensively for **burn wounds**
- Rare SEs include: **hemolysis** in G6PD patients, **methemoglobinemia**, renal insufficiency, **argyria**, leukopenia, and unmasking porphyria

## Iodoquinol

- Quinolone-derivative with high iodine concentration
- Activity against GP and GN and dermatophytes/yeasts

## Benzoyl peroxide

- Broad-spectrum antibacterial agent that functions via strong oxidizing properties (good vs *P. acnes*) – **no bacterial resistance reported to date**
- Used for acne (alone and in combination with topical antibiotics and adapalene); has keratolytic properties
- When used with certain formulations of tretinoin, can → oxidation/degradation of retinoid agent
- Most common SE is local irritation; can bleach hair/fabric

## Metronidazole

- Nitroimidazole that disrupts DNA synthesis

- Activity against **protozoa** and **anaerobes**; not active against *P. acnes*, staphylococcus, streptococcus, fungi, or *Demodex*
- Pregnancy category **B**; used primarily for rosacea (likely because of its antiinflammatory properties)

### Azelaic acid

- **Dicarboxylic acid** that disrupts mitochondrial respiration, ↓DNA synthesis (especially in abnormal melanocytes), and ↓ROS production by PMNs
- Also competitively **inhibits tyrosinase** → ↓**pigmentation**
- Activity against *P. acnes*; used in acne and rosacea (including perioral dermatitis)
- May be used in acne and hyperpigmentation disorders (e.g., melasma and PIH)

### Sodium sulfacetamide

- Activity against *P. acnes*
- **Inhibits bacterial dihydropteroate synthetase** (prevents conversion of PABA → folic acid) → ↓nucleic acid/protein
- Used in acne and rosacea as a combination agent with or without precipitated sulfur

## Systemic antibacterial agents

### Penicillins

- MoA: β-Lactam ring binds to bacterial enzyme DD-transpeptidase → inhibits formation of **peptidoglycan cross-links** in the bacterial cell wall → **cell wall breakdown**
- Many are susceptible to β-lactamases
- Generations
  - First: dicloxacillin, oxacillin
    - Good for GP cocci, like MSSA
  - Second: aminopenicillins (ampicillin and amoxicillin)
    - GN bacilli and GP cocci
    - Amoxicillin has fewer GI SEs
    - **Ampicillin + mononucleosis/allopurinol/lymphocytic leukemia → generalized morbilliform itchy eruption** starting 1 week after antibiotic initiation
    - May be associated with allergic reactions
  - Third and Fourth: carboxypenicillins (carbenicillin) and ureidopenicillins (piperacillin)
    - Antipseudomonal activity
  - Combination β-lactam + β-lactamase inhibitor
    - Amoxicillin-clavulanate, ampicillin-sulbactam (IV), ticarcillin-clavulanate (IV), and piperacillin-tazobactam (IV)
    - **β-lactamase inhibitors inhibit β-lactamase** → allows the β-lactam antibiotic to function – helpful in MSSA, *Haemophilus*, *Klebsiella*, *E. coli*, *Proteus*, and *B. fragilis* infections
    - Good for polymicrobial infections (e.g., **amoxicillin-clavulanate is the treatment of choice for animal or human bites**;

ticarcillin-clavulanate good for **diabetic foot ulcers** and burn wounds)

- Ticarcillin/piperacillin → hypernatremia, ↑LFTs, neutropenia, and ↑bleeding times
- ↑risk of cholestatic injury with amoxicillin/clavulanate
- Good for various common streptococci (treat β-hemolytic streptococci for at least 10 days to prevent possible rheumatic fever) and MSSA skin infections (e.g., erysipelas, cellulitis, impetigo, folliculitis, furunculosis, and ecthyma)
- Other uses include SSSS (**IV nafcillin**), syphilis (**IM injection of penicillin G**), erysipeloid, cutaneous anthrax, Lyme disease, and leptospirosis
- SEs: hypersensitivity reactions (common association; **2% of cephalosporin-allergic patients are penicillin-allergic**), GI SEs (common), hematologic SEs, sore nails (dicloxacillin), onychomadesis/photo-onycholysis (cloxacillin), interstitial nephritis (very rare), and AGEP
- **Probenecid prolongs renal excretion** → ↑penicillin levels (also can ↑cephalosporin levels)

### Cephalosporins

- MoA similar to penicillins as structure is β-lactam ring + 6-membered dihydrothiazine ring
- Resistant to β-lactamases
- Generations
  - First: cefadroxil and cephalexin
    - Best for GP cocci, but not good for MRSA or penicillin-resistant *S. pneumonia*
  - Second: cefaclor and cefuroxime
    - More GN activity and less GP activity
    - Good for *H. influenzae*, *M. catarrhalis*, *N. meningitidis*, and *N. gonorrhoeae*
    - Cephamycins (cefoxitin and cefotetan) are good for *B. fragilis*
  - Third: cefixime, cefdinir, cefotaxime, ceftazidime, cefepodoxime, and ceftriaxone
    - Good GN activity, but not GP activity
    - Some good for *P. aeruginosa* (i.e., **ceftazidime**)
    - Good for soft tissue abscesses and **diabetic foot ulcers**
  - Fourth: cefepime (IV)
    - Broad coverage – MSSA, nonenterococcal streptococci, and GNs (including *P. aeruginosa*)
  - Fifth: ceftaroline (IV)
    - MRSA, VISA, hVISA, VRSA, MSSA, and CNS
    - Good for acute bacterial skin infections
- Oral cephalosporins used frequently in dermatology for uncomplicated skin and soft tissue infections; may need IV agents for complicated cellulitis or necrotizing fasciitis
- SEs: GI symptoms (most common), hypersensitivity reactions (**cross-reactivity in ≈ 5%–10% of penicillin-allergic patients**), *Candida* infections, hematologic SEs (e.g., hemolytic anemia – cefotetan most common), ↑LFTs, **serum sickness-like reaction (cefaclor)**, Jarisch-Herxheimer reaction (in Lyme disease patients receiving cefuroxime axetil), disulfiram-like reaction (cefotetan), and AGEP

- Do not give w/ aminoglycosides → ↑risk of nephrotoxicity

## Vancomycin

- MoA: tricyclic glycopeptide that inhibits bacterial cell wall synthesis
- Only works for GP organisms – most important use in dermatology is against MRSA skin and soft tissue infections
- SEs: **red man syndrome**, **LABD** (most common cause of drug-induced LABD; as a result of IgA antibodies to LAD285 and IgA/IgG to BP180), **hearing loss** (patients with renal failure), and **nephrotoxicity** (if given with aminoglycosides)

## Macrolides

- MoA: bind to **50s subunit** of bacterial ribosome → ↓protein synthesis; also has antiinflammatory properties
- Good for GP, except MRSA and enterococcus – used in dermatology for skin and soft tissue infections
  - Erythromycin
    - Not used as commonly these days because of ↑resistance (particularly *S. aureus*) and GI SEs
    - Some indications include: Lyme disease, erythrasma/pitted keratolysis, anthrax, erysipeloid, chancroid, and LGV
    - May be used for acne, rosacea, and pityriasis rosea
    - **Potent CYP3A4 inhibitor** (e.g., monitor use of warfarin, mexiletine, theophylline, and statins [↑rhabdomyolysis])
    - SEs: **GI symptoms** (most common and dose-limiting), ototoxicity/hear loss, **QT prolongation/torsades de pointes** (worse when given with terfenadine, astemizole, cisapride, and certain quinolones), and hypersensitivity reactions; **erythromycin estolate in pregnancy may → hepatotoxicity (intrahepatic cholestasis) in mother**; possible association of cardiovascular malformation and **pyloric stenosis** if fetus exposed *in utero*
  - Azithromycin
    - **Better than erythromycin for GPs** (→ often used as second line prophylactic antibiotic in dermatology surgery for PCN/CSN-allergic patients); has some GN activity (*E. coli*, *N. gonorrhoeae*, *H. ducreyi*, and *C. trachomatis*)
    - Activity against *P. multocida* (animal bites), *E. corrodens* (human bites), and atypical mycobacteria, *T. pallidum*, *B. burgdorferi*, *T. gondii*, and *K. granulomatis* (granuloma inguinale)
    - Has been used for acne
    - SEs: deafness, angioedema, photosensitivity, hypersensitivity, and contact dermatitis; antacids can ↓absorption
  - Clarithromycin
    - Better than erythromycin for GPs
    - CYP3A4 inhibitor (less potent than erythromycin)
    - Has activity against some GNs, atypical mycobacteria (good activity against *M. leprae*), *T. pallidum*, *B. burgdorferi*, and *T. gondii*

- SEs: metallic/bitter taste, fixed drug eruption, LCV, and hypersensitivity reactions; contraindicated in renal dysfunction

## Fluoroquinolones

- MoA: **inhibits DNA gyrase** (bacterial topoisomerase II) +/- **topoisomerase IV** → DNA fragmentation
  - DNA gyrase is predominant target in GN; whereas topoisomerase IV is target in GP
- First- and second-generation quinolones (ciprofloxacin, ofloxacin, and nalidixic acid): only target DNA gyrase (topoisomerase II) → only effective against GN
- Third- and fourth-generation quinolones (levofloxacin, moxifloxacin, sparfloxacin, and gatifloxacin): target both topoisomerase forms (IV > II) → ↑GP coverage and ↓bacterial resistance; slightly ↓efficacy against GN
- Good for GNs, like *P. aeruginosa* (especially ciprofloxacin); may be used with some GPs like *S. aureus* and *S. pyogenes* (primarily third- and fourth-generation quinolones); **ciprofloxacin is the treatment of choice for cutaneous anthrax (*B. anthrax*)**; various fluoroquinolones effective for mycobacterial infections
- Generally **excreted renally**, except for moxifloxacin
- Used in dermatology to treat GN skin and soft tissue infections, some GP skin/soft tissue infections, GN toe web-space infections, diabetic foot ulcers, and GN folliculitis
- SEs: GI symptoms (#1), CNS SEs (headache, dizziness, seizures, psychosis, and depression), **tendinitis/tendon rupture**, hypersensitivity (especially ciprofloxacin), and **photosensitivity/photo-onycholysis** (**lomefloxacin, enoxacin, and sparfloxacin >> ciprofloxacin > norfloxacin > ofloxacin >> levofloxacin**)
  - Photosensitivity is from the **UVA spectrum** (and visible spectrum for sparfloxacin)
  - **Levofloxacin NOT** associated with photosensitivity
- Administration with divalent cations (calcium, magnesium, aluminum, and zinc) → ↓absorption
- CYP1A2 inhibitors (caution with warfarin, theophylline, caffeine, antiarrhythmics (↑QT/torsades), zileuton, and beta blockers); also caution with cyclosporine (in setting of organ transplant, can → ↑creatinine levels)

## Tetracyclines

- MoA: binds **30s subunit** of bacterial ribosome → ↓protein synthesis; antiinflammatory properties (e.g., **inhibits multiple matrix metalloproteinases**, neutrophil migration, and ↓innate cytokines)
- Main uses in dermatology: acne, perioral dermatitis, rosacea, immunobullous diseases (e.g., bullous pemphigoid), **CARP (minocycline)**, cutaneous sarcoidosis/other **granulomatous diseases** (**minocycline**), acne keloidalis nuchae, PLEVA/PLC, and **acneiform eruptions 2° to EGFR inhibitors**
- Also useful for various GP and GN skin infections, including **MRSA** (doxycycline and minocycline) and those caused by *Chlamydia* spp. (**doxycycline is the treatment of choice in LGV**), *Rickettsia* spp. (**doxycycline is the treatment of choice for rickettsial and rickettsial-like infections** – RMSF, rickettsialpox,



Q fever, trench fever, and ehrlichiosis), *Mycoplasma* spp., atypical mycobacteria, spirochetes (syphilis [if patient is PCN-allergic], and Lyme disease – doxycycline is the treatment of choice in early disease)

- **Subantimicrobial doses**, like doxycycline modified-release (40 mg per day) or extended-release minocycline (various doses) **effective for rosacea and acne**, and **do NOT ↑bacterial resistance**; may also have ↓rate of vaginal candidiasis
- Bacterial resistance via ribosomal protection and/or drug efflux
- Lipophilic (**minocycline** > doxycycline > tetracycline)
- Various **metallic cations** (e.g., calcium, iron, zinc, magnesium, bismuth, and aluminum) can ↓**absorption via chelation** (tetracycline > doxycycline > minocycline)
  - Found in products like antacids, laxatives, dairy, and supplements
- SEs: **GI symptoms** (esophagitis, nausea, and abdominal pain; most common with doxycycline, but less so with enteric-coated form), acute vestibular SEs (dizziness and vertigo; usually with minocycline), benign intracranial hypertension/**pseudotumor cerebri** (usually minocycline; ↑risk if given w/ isotretinoin), **photosensitivity/photonychia** (demeclocycline > doxycycline > tetracycline > minocycline), hyperpigmentation of skin/nail beds/teeth/mucous membranes/bone (minocycline), vaginal candidiasis, **GN acne/folliculitis**, serum sickness-like reactions (minocycline), drug-induced Sweet's syndrome (minocycline), autoimmune hepatitis (minocycline), DRESS/DHS (minocycline), lupus-like syndrome (minocycline; usually ANA+ and antihistone AB+), and cutaneous PAN/**vasculitis** (**minocycline**; pANCA+)
- Minocycline hyperpigmentation types:
  - Type 1: Blue-gray in sites of **facial scarring** – stains for iron and melanin
  - Type 2: Blue-gray on **shins** and/or forearms – stains for iron and melanin
  - Type 3: **Diffuse** muddy brown on **sun-exposed skin** – stains melanin only; represents a low-grade phototoxic eruption with PIH
- Pregnancy category D → affects fetal teeth/bones; debatable ↓in OCP efficacy
- **Food decreases absorption**, more so in tetracycline than doxycycline or minocycline
- Do not give to **patients under 8 years old** → **tooth discoloration**
  - Tetracycline and minocycline can also induce **adult-onset tooth pigmentation**
- Tetracyclines excreted renally, **except** doxycycline (mainly via GI tract – so can be used in renal failure)

## Rifampin

- MoA: binds β-subunit of bacterial **DNA-dependent RNA polymerase** → ↓RNA/protein synthesis
- Effective against various mycobacteria (e.g., *M. tuberculosis*, *M. leprae*, and *M. marinum*) and some other GP and GN organisms (e.g., staphylococcus)

- **Do NOT give as monotherapy, because of rapid development of resistance**
- **Major CYP450 inducer** → ↑drug clearance/↓efficacy (e.g., OCPs, warfarin, azoles, CCBs, statins, and cyclosporine)
- Dermatologic uses: mycobacterial infections (part of multidrug therapy), *Bartonella* infections (e.g., cat-scratch disease and bacillary angiomatosis), MRSA/MSSA, rhinoscleroma, and cutaneous leishmaniasis
- SEs: **orange-red discoloration of body fluids**, CNS (headache and drowsiness), GI symptoms, development of rifampin-dependent antibodies (can → anaphylaxis, flu-like symptoms, renal failure, and hemolytic anemia), hepatotoxicity (especially w/ isoniazid), DVTs, pulmonary fibrosis, ocular SEs, **worsening of porphyria (induces δ-ALA synthetase)**, and possible hemorrhagic disease of the newborn and mother in pregnancy

## Trimethoprim-sulfamethoxazole (aka cotrimoxazole)

- Dihydrofolate reductase inhibitor (trimethoprim) + dihydropteroate synthetase inhibitor (sulfamethoxazole) → ↓**tetrahydrofolic acid** → ↓**bacterial nucleic acid/protein synthesis**
- Effective against various GP cocci (e.g., MRSA, *E. faecalis*, and *S. pyogenes*), *H. influenzae*, *P. jirovecii*, *Nocardia* spp., *Chlamydia*, and various GNs
- Dermatologic uses: acne, hidradenitis suppurativa, **granuloma inguinale**, actinomycetoma, cat-scratch disease, and chronic melioidosis (*Burkholderia pseudomallei*)
- Caution in patients w/ renal insufficiency as it is primarily renally cleared
- SEs: most commonly GI and CNS, but also antibiotic-associated colitis, hypersensitivity reactions (cutaneous eruptions much more common in HIV patients; TMP/SMX accounts for 30% of SJS/TEN cases), hematologic SEs (agranulocytosis, thrombocytopenia, folate deficiency + megaloblastic anemia, neutropenia, and hemolytic anemia in patients w/ G6PD deficiency)
- Pregnancy category C – can result in jaundice, hemolytic anemia, and kernicterus of baby if taken in third trimester
- Can ↑dapsone levels, ↑**hematologic toxicity in patients taking MTX (both ↓THF)**, ↑renal toxicity in patients taking cyclosporine, ↑K<sup>+</sup> in patients on ACEIs/ARBs

## Clindamycin

- Lincosamide that binds to **50S subunit** of bacterial ribosomal RNA → ↓ribosomal translocation/protein synthesis
- Effective against **GP cocci** (e.g., *Staphylococcus* spp. and *Streptococcus* spp.) and **anaerobes** (*Bacteroides* spp. and *C. perfringens*), but not usually GNs (except *Capnocytophaga canimorsus*)
  - **"D zone" test** helps determine whether inducible resistance is present in an erythromycin-resistant, clindamycin-sensitive organism (bacteria with *erm* gene)

- Dermatologic uses: skin and soft tissue infections (e.g., staphylococci, MRSA, and MSSA), including some deep soft tissue infections (e.g., streptococcal myositis, *C. perfringens* infection, and diabetic foot ulcers)
- SEs: **antibiotic-associated colitis**, rashes, and rare bone marrow suppression may ↑ neuromuscular blocking

### Linezolid

- MoA: binds 23S portion of 50S ribosomal subunit of bacteria
- Good for skin infections caused by staphylococcus (including MRSA) and streptococcus
- Typically not first line, but good for resistant cases
- SEs: myelosuppression in 2%, **serotonin syndrome** (if given with serotonergic drugs like SSRIs, MAOIs, and tricyclics), and optic/peripheral neuropathy

### Quinupristin and dalbapristin

- MoA: diffuses through bacterial cell wall and binds 50S ribosomal subunit sites → ↓ protein synthesis
- Used in complicated skin and soft tissue infections caused by GPs (e.g., MRSA and VRE)
- Can cause anaphylaxis, angioedema, and ↑ bilirubin
- Potent CYP3A4 inhibitor

### Daptomycin

- MoA: depolarizes bacterial cell membrane → cell death
- Good for complicated skin and soft tissue infections caused by GPs (e.g., MRSA, VRE, and linezolid-resistant GPs)
- SEs: neuropathy, myopathy (check CPKs; caution w/ statins), eosinophilic pneumonia, and nephrotoxicity

### Others

- Some new antibiotics for complicated skin infections include: telavancin, tigecycline, dalbavancin, and oritavancin

## Antiviral agents

### Acyclovir

- Guanosine analog that requires:
  - Phosphorylation first by **herpes-specific thymidine kinase** → acyclovir monophosphate
  - Subsequent phosphorylation by human cellular GMP kinase and other cellular kinases → **acyclovir triphosphate**
    - At this stage, it competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase → incorporates into viral DNA → **chain terminates** and ↓ viral duplication
- Penciclovir also works in this fashion
- Valacyclovir and famciclovir are prodrugs of (and converted to) acyclovir and penciclovir, respectively, so they are also dependent on these enzymes and pathways

- Topical and systemic forms available; pregnancy category B
  - Topical form only approved for HSV, not VZV
- Dermatologic uses: herpes simplex infections, varicella zoster, and recurrent EM 2° to HSV
  - Consider suppressive doses in HSV patients if >6 outbreaks per year
  - IV form used in cases of disseminated HSV/VZV, eczema herpeticum, and in immunosuppressed patients
- Low rate of SEs and interactions:
  - IV infusions rarely associated with renal impairment (2° to **crystalline nephropathy**)
  - AZT + acyclovir can → drowsiness/lethargy
  - **Probenecid** → ↑ bioavailability and ↓ renal clearance
- If **viral resistance** occurs (via mutations in thymidine kinase, or less commonly in DNA polymerase) → use **foscarnet** or **cidofovir**
  - Patients resistant to acyclovir will also be resistant to valacyclovir, famciclovir and penciclovir

### Valacyclovir

- Prodrug of acyclovir with great bioavailability (almost as much as IV acyclovir); oral and topical forms
- Same uses as acyclovir with excellent SE profile
  - Rarely can cause TTP/HUS in HIV patients

### Famciclovir and penciclovir

- Famciclovir is prodrug of penciclovir
  - Famciclovir available orally, but penciclovir only available topically
  - Penciclovir triphosphate has significantly longer half-life than acyclovir triphosphate
  - Famciclovir has even better bioavailability than valacyclovir
  - Famciclovir and valacyclovir **more effective at ↓ VZV pain than acyclovir**
  - Indications:
    - Famciclovir: same indications as acyclovir/valacyclovir
    - Penciclovir: herpes labialis only

### Cidofovir

- Nucleoside phosphate analog of deoxycytidine monophosphate effective in HPV, HSV, CMV retinitis ("Cidofovir = CMV"), orf, and molluscum
  - Must be phosphorylated twice, to cidofovir diphosphate, in order to be active
  - **Does NOT require viral thymidine kinase** like previously mentioned agents
  - Once active, acts as a competitive inhibitor and alternate substrate for viral DNA polymerases → incorporates into DNA strand → blockage/termination of DNA synthesis
- IV and topical forms available (topicals are not commercially available, however)
- SEs: nephrotoxicity (most common), neutropenia, alopecia, uveitis/iritis, and cardiomyopathy



## Foscarnet

- An intravenous pyrophosphate analog that binds to **pyrophosphate-binding site on viral DNA polymerase** → inhibition of pyrophosphate cleavage from deoxyadenosine triphosphate → disruption of DNA elongation
- **Treatment of choice for acyclovir-resistant HSV** (does not require same enzymes as acyclovir and penciclovir); also used to treat CMV retinitis and CMV skin infection in HIV patients
- SEs: **penile erosions (boards favorite)**, thrombophlebitis, nephrotoxicity, seizures, and electrolyte disturbances

## Bleomycin

- Chemotherapeutic agent that can be used intralesionally for warts
- MoA: binds DNA → single strand breaks → ↓protein synthesis → ↑apoptosis/necrosis of keratinocytes
- SEs: **injection pain**, **Raynaud's phenomenon**, loss of nail plate/nail dystrophy, and **flagellate hyperpigmentation**

## Podophyllin and podofilox (0.5% podophyllotoxin)

- Podophyllin administered in office and its derivative podofilox administered at home by patient
  - Podofilox is safer – fewer mutagens; pregnancy category C
- Antimitotic agent that **binds tubulin** → cell cycle arrest in metaphase
- FDA approved for genital warts
- SEs are typically local (DO NOT use in pregnancy – teratogenic)

## Cantharidin

- Blistering agent (comes from blister beetle/**Spanish fly**, *Lytta vesicatoria*)
- MoA: disrupts desmosomes → intraepidermal acantholysis → bullae
- Applied in office under occlusion for warts/molluscum; washed off at home 4 hours later
- SEs: pain from blister and **ring wart** formation

## Sinecatechins

- Green tea (*Camellia sinensis*)-derived polyphenol **epigallocatechin gallate** → apoptosis, inhibition of telomerase, and an antioxidant effect on cells
- Approved for genital/perianal warts; SEs are local (e.g., upain, itch, and swelling)

## 5-fluorouracil and imiquimod (discussed in the section 2.5)

## Antifungal agents

### I. Azoles

- MoA: **inhibit 14 $\alpha$  demethylase** (catalyzes conversion of lanosterol to ergosterol) → ↓ergosterol →

↓cell membrane synthesis, ↑ membrane rigidity/permeability, growth inhibition, and cell death

### Itraconazole

- Metabolized mainly in liver (CYP3A4); **absorption enhanced in an acidic environment**
- FDA approved indications: dermatophyte onychomycosis (12 week 200 mg/day course for toenails), oropharyngeal/esophageal candidiasis, **blastomycosis**, **histoplasmosis**, and aspergillosis refractory to amphotericin B
- Off-label dermatologic uses: other tinea infections, candida infections, **extensive tinea versicolor** (for very short courses or even single doses), and nondermatophyte/saprophytic onychomycosis
- Contraindications:
  - Ventricular dysfunction and CHF
  - Active liver disease or h/o liver toxicity with other drugs
  - Concurrent use of certain drugs metabolized via CYP3A4 (e.g., **pimozide**, **quinidine**, and **cisapride**) as it is a CYP3A4 inhibitor
  - Concurrent use with **levomethadyl**, **dofetilide**, **statins**, **midazolam**, **triazolam**, **nisoldipine**, and **ergot alkaloids**
- Common SEs: GI (e.g., nausea, vomiting, and abdominal pain), cutaneous (e.g., rash – more common if also using immunosuppressive meds), neurologic (e.g., headache), edema, ↑LFTs, rhinitis, and fever
- Rarer SEs: hearing loss, peripheral neuropathy, CV events (e.g., CHF), dysgeusia, pancreatitis, hepatotoxicity, neutropenia/leukopenia, pulmonary edema, and hypokalemia

### Fluconazole

- Very little hepatic metabolism; pregnancy category D
- FDA approved for **vaginal/oropharyngeal/esophageal candidiasis** and **cryptococcal meningitis**
- Off-label dermatologic uses: tinea infections, systemic *Candida* infections, cutaneous candidiasis, **coccidioidal meningitis**, and onychomycosis (150–300 mg once a week for 3–6 months in fingernails and 9–12 months in toenails; ≈ 40%–50% clinical cure rate; also good for nondermatophyte types, such as *Scopulariopsis* and *Candida*)
- Contraindications:
  - **Potent CYP2C9 inhibitor** – caution with substrates
  - Do NOT administer with pimozide, quinidine, cisapride, **erythromycin**, terfenadine, astemizole, voriconazole, or statins
- Common SEs: GI (e.g., nausea and abdominal pain), skin rash, and headache
- Rare SEs: CV events (e.g., torsades), cholestasis/hepatocellular damage/liver failure, severe skin reactions, seizures, leukopenia/thrombocytopenia, dysgeusia, and hyperlipidemia

### Ketoconazole

- Systemic form not commonly used today because of the associated high rate of **hepatic toxicity**
  - If used, typically <10 days
- FDA approved for tinea corporis/cruris/pedis/capitis, chronic mucocutaneous candidiasis, vaginal and

cutaneous candidiasis, chromoblastomycosis, blastomycosis, histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis

- Topical uses: tinea infections, cutaneous candidiasis, tinea versicolor, and seborrheic dermatitis
- Do NOT administer with **cisapride, terfenadine, or astemizole**, as interaction can → serious CV events like **↑QT syndrome**
- SEs (systemic form only): GI symptoms, idiosyncratic hepatotoxicity, pruritus, and urticaria

### Voriconazole

- New generation of azoles used primarily for serious, invasive fungal infections in immunosuppressed hosts (**invasive aspergillosis**, *Candida* infections, and *Fusarium* infections)
- Unique SEs: **severe phototoxicity** (including **pseudoporphyria**, and **xeroderma pigmentosum-like changes**) and **↑risk SCC**, visual disturbances (e.g., blurriness), hepatotoxicity, GI issues, and QT prolongation

### Miconazole, clotrimazole, and econazole

- Topical azoles active against various dermatophytes, *M. furfur*, and *C. albicans*
- Good for tinea infections, tinea versicolor, and cutaneous candidiasis

### Efinaconazole

- Novel solution formulation for onychomycosis – daily 48-week course – only 15% to 20% complete cure

### Luliconazole

- A new once-daily 1% cream used for short courses to treat various cutaneous tinea infections (e.g., 2 week treatment for interdigital tinea pedis)
- Other topical antifungals good for cutaneous dermatophyte infections and possibly cutaneous *Candida* infections include oxiconazole, sulconazole, and sertraconazole

## II. Allylamines/benzylamines

- MoA: **inhibit squalene epoxidase** (catalyzes conversion of squalene to lanosterol) → ↓cell membrane synthesis

### Terbinafine (Lamisil®)

- Oral and topical formulations
- Metabolized mainly in liver – do NOT give in active liver disease; also do not give if CrCl ≤50 mL/min
- FDA approved for dermatophyte onychomycosis and tinea capitis (granule formulation)
- Off-label dermatologic uses (systemic formulation): other tinea infections, subcutaneous/systemic mycoses (e.g., histoplasmosis and chromoblastomycosis), and other types of onychomycosis (good for *Aspergillus*, but not *Candida*)
- Topical formulation: utility limited to superficial dermatophyte infections
  - More effective than clotrimazole and oxiconazole for tinea pedis

- 6 week 250 mg/day course for fingernail onychomycosis and 12 week 250 mg/day course for toenail onychomycosis (clinical cure ≈ 60%–70%)
- Tinea capitis:
  - Highly effective against **endothrix** organisms (most commonly *T. tonsurans*)
  - Less effective against **ectothrix** organisms like *M. canis* (**griseofulvin preferred**)
- Most common SEs: GI (e.g., diarrhea), cutaneous (e.g., rash), headache, and ↑LFT
- Rarer SEs: **taste/smell disturbance**, severe skin reactions (e.g., SJS/TEN), visual disturbance, **hepatobiliary dysfunction/hepatitis/liver failure (idiosyncratic)**, hematologic abnormalities (e.g., neutropenia or thrombocytopenia), rhabdomyolysis, **depression**, **exacerbation of SLE**, **drug-induced SCLE**
- **Inhibits CYP2D6**, so exercise caution if giving with CYP2D6 substrates (e.g., doxepin or amitriptyline)

### Naftifine (Naftin®)

- Topical formulation only – effective for dermatophyte infections primarily (may be more effective than azoles in treatment of **cutaneous dermatophytoses**)

### Butenafine (Mentax®)

- Benzylamine class topical antifungal effective in cutaneous dermatophyte infections, tinea versicolor, and cutaneous candidal infections

## III. Griseofulvin

- FDA approved for dermatophyte onychomycosis and tinea corporis/cruris/pedis/capitis
  - **More effective in tinea capitis caused by *Microsporum* (e.g., *M. canis*) than terbinafine**
- SEs: GI disturbance and headache are most common; FDE, photosensitivity, and exfoliative dermatitis; can instigate or worsen porphyria and lupus
- MoA: **interferes with tubulin** → inhibition of mitosis; binds to keratin in keratin precursor cells → resistance to fungal infections

## IV. Ciclopirox olamine (Loprox®)

- MoA: disrupts fungal cell membrane transport of important molecules, ↓cell membrane integrity, inhibits cellular respiratory enzymes, and blocks important enzymatic cofactors
- Topical formulations only – cutaneous dermatophyte infections, *Malassezia* spp., tinea versicolor, cutaneous candidiasis, and onychomycosis (in lacquer form)
  - Ciclopirox and topical azoles are superior to allylamine/benzylamine drugs for *Candida*

## V. Selenium sulfide

- Topical formulations only – tinea versicolor, seborrheic dermatitis of scalp, and CARP

## VI. Nystatin

- Polyene topical agent that **binds *Candida* cell membrane sterols** → ↑ permeability → cell death
- Used for cutaneous/mucosal *Candida* infections

## VII. Echinocandins (caspofungin, micafungin, and anidulafungin)

- MoA: **inhibit  $\beta$ -(1,3)-D-glucan synthase** → ↓ glucan production → disrupt cell wall synthesis
- Used primarily in invasive *Candida* infections and invasive aspergillosis (second line)
- Unique SEs: facial swelling (caspofungin), ↑ alkaline phosphatase (caspofungin), hypokalemia (caspofungin), and hematuria/proteinuria (caspofungin)

## Antiparasitic agents

(Table 2-5 and Table 2-6)

- Interesting facts about drugs not in the tables: benzyl benzoate may → disulfiram-like reaction; **precipitated sulfur is safe in pregnant women with scabies**, but so is **permethrin**; topical thiabendazole compound may be helpful for cutaneous larva migrans

## 2.7 PHOTOTHERAPY

- Divided into ultraviolet A (UVA) (320–400 nm) and ultraviolet B (UVB) (280–320 nm) modalities

**Table 2-5.** Systemic Antiparasitic Treatments

Agent	Mechanism	Uses	Side Effects
<i>Ivermectin</i>	Binds <b>glutamate-gated chloride ion channels</b> of parasite nerve/muscle cells → ↑ membrane permeability → hyper-polarization → death Of note, resistance can occur due to SNPs of P-glycoprotein-like protein	FDA: onchocerciasis, intestinal strongyloidiasis (secondary to <i>Strongyloides stercoralis</i> ) Off-label: scabies (less effective in crusted form), cutaneous larva migrans, and pediculosis	Commonly rashes, pruritus, fever, and lymphadenopathy (less with scabies infection) Rarely death and encephalopathy when used in patients with loiasis <b>Mazzotti reactions</b> = rash/systemic symptoms/ocular reactions; occurs in patients with <b>onchocerciasis</b> → doxycycline helps reduce these reactions
<i>Albendazole</i>	Stops <b>tubulin polymerization</b> → immobilization and death of parasite	FDA: neurocysticercosis and hydatid disease Off-label: <i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Enterobius vermicularis</i> , <i>Ancylostoma duodenale</i> and <i>Necator americanus</i> (hookworms), <i>Taenia</i> , <i>Strongyloides stercoralis</i> , <i>Giardia</i> , scabies	Bone marrow suppression (↑ risk if patient has liver disease), aplastic anemia, agranulocytosis, hepatotoxicity, GI SEs, rash May ↑ theophylline levels Resistance higher in patients with HTLV-1 infection
<i>Thiabendazole</i>	Inhibits <b>fumarate reductase</b>	FDA: strongyloides, cutaneous larva migrans, and visceral larva migrans Off-label: trichinosis, uncinariasis, <i>Necator</i> , <i>Ancylostoma</i> , trichuriasis, and ascariasis	Hepatotoxicity, GI SEs, CNS SEs, SJS May ↑ theophylline levels

**Table 2-6.** Topical Antiparasitic Treatments

Agent	Mechanism	Uses	Side Effects
Permethrin	Related to pyrethrins, which come from flowers of genus <b><i>Compositae</i></b> Disables sodium transport channels on cell membranes of arthropods → paralysis	Scabies (5% cream is the treatment of choice; neck down application – 2 overnight applications separated by 1 week) and <i>Pediculosis capitis</i> (1% cream rinse)	Local SEs
Malathion	<b>Organophosphate</b> that inhibits acetylcholinesterase in arthropods → neuromuscular paralysis	<i>Pediculosis capitis</i> (0.5% lotion; most effective treatment in the United States; treatment of choice in children ≥ 6 years old)	Local SEs Potentially <b>flammable</b> Malodorous If ingested → symptoms of <b>organo-phosphate poisoning</b> /↓ cholinesterase
Spinosad	Instigates arthropod motor neurons → paralysis	<i>Pediculosis capitis</i> (very rapid effect – 10 minute application)	Local SEs
Lindane	Organochlorine → ↓ neurotransmission → arthropod respiratory/muscular paralysis	Scabies and <i>Pediculosis capitis</i>	<b>Seizures</b> if ingested or multiple applications Aplastic anemia, leukemia

- Doses of light determined by skin type usually or 70% of minimum erythema dose (MED; lowest dose that results in minimally visual erythema) and increased as tolerated each visit up to a maximum dose

## UVA modalities

### Psoralen plus UVA (PUVA)

- Photochemical reaction between psoralen (8-methoxypsoralen usually) and UVA
  - Psoralen (0.4–0.6 mg/kg 1–2 hours before UVA) can be administered orally or topically
    - Of note, before UV exposure, **psoralen intercalates into DNA**
    - Photoactivated psoralen molecules form 3,4 or 4',5' cyclobutane monofunctional adducts to pyrimidines in DNA → interstrand DNA cross-link → ↓DNA synthesis/cell cycle arrest
    - PUVA → selective immunosuppression, selective cytotoxicity (via production of ROS and free radicals), and melanocyte stimulation
    - Psoralens ideally taken fasting, because food slows absorption
    - Absorption and bioavailability vary widely with 8-methoxypsoralen (8-MOP)
    - Metabolized by liver
    - Used in many dermatoses including psoriasis, vitiligo, CTCL, dermatitis, photodermatoses (using desensitization protocols), GVHD, and lichen planus
    - SEs include: nausea/vomiting (food may help), **phototoxic reactions** (e.g., symptomatic erythema [if widespread, hold treatment] and pruritus), hepatic toxicity, bronchoconstriction, herpes simplex recurrences, cardiovascular stress, CNS disturbances, photoaging, melanoma, and NMSC (SCC>>BCC; usually if ≥250 treatments; skin examinations every 6–12 months), and ocular issues (e.g., **cataracts**)
    - UV-opaque goggles and face/genital protection in unit; UV-opaque glasses after exposure until sunset, along with good photoprotection
    - Contraindications: lactation and certain skin disorders (lupus erythematosus, pemphigus/pemphigoid, albinism, porphyria, and XP)
  - Treatments administered two to three times per week initially till mostly clear, then a maintenance schedule where radiation dose is kept the same and visit frequency slowly decreased (even to one treatment a month), then stopped
  - Safe in combination with other treatments (e.g., topicals, MTX, acitretin, and UVB)

### UVA-1 (340–400nm)

- Treatments can be low, medium, or high dose
- Dose based on MED as sensitivity to UVA-1 can vary greatly between people
- Not many centers in the United States have UVA-1 units and not necessarily superior to PUVA and/or NB-UVB

- Various skin disorders including SLE (low dose), **scleroderma**/other sclerodermoid skin conditions (need at least 30 treatments), atopic dermatitis, and MF
- SEs include erythema in the short-term; no long-term studies for SEs

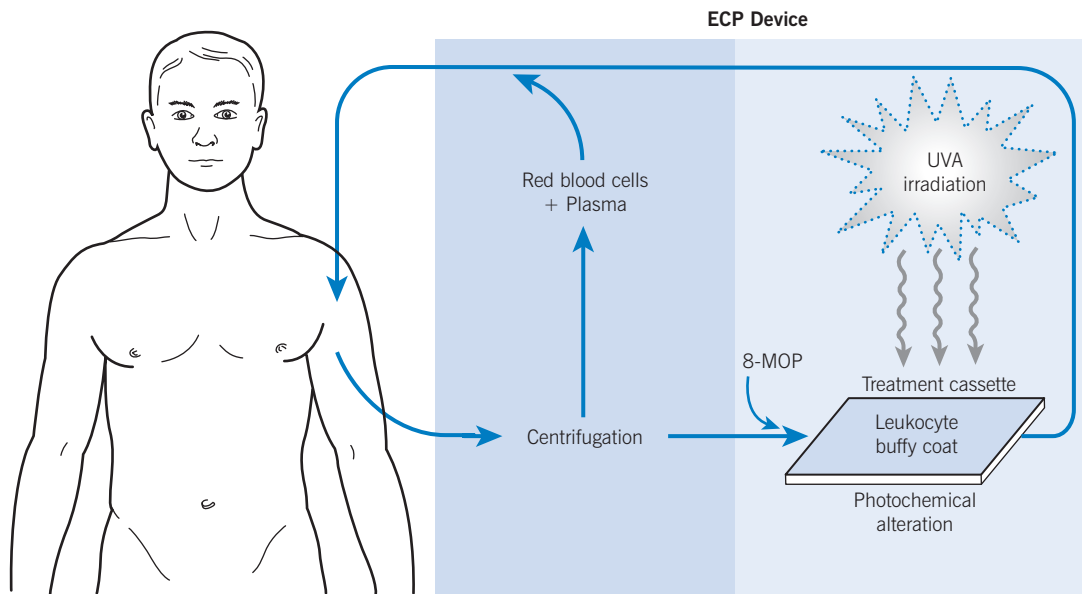
## UVB modalities

- MoA: ↓DNA synthesis (i.e., in psoriatic epidermis) and ↑p53 → cell cycle arrest/keratinocyte apoptosis; ↓proinflammatory cytokines, ↓Langerhans cells in skin
- **Narrowband UVB (311–313 nm)**
  - Treatments given 3×/week initially (based on skin type or 70% MED) and increased by 10–15% each treatment; may have to adjust dose based on erythema severity
  - UV-opaque goggles during treatment and covering face/genitals
  - SEs: skin reactions (e.g., erythema or pruritus), mucosal reactions (recurrent herpes labialis, or blepharitis), exacerbation of SLE and blistering disorders, and NMSC (lower risk than BB-UVB or PUVA)
  - Used in psoriasis (most commonly prescribed phototherapy), **vitiligo (treatment of choice)**, mycosis fungoides (patch and plaque), atopic dermatitis, photodermatoses (using desensitization protocols), and pruritus (idiopathic and secondary)
  - Similar contraindications to PUVA
- **Broadband UVB** – 280–320 nm; more convenient in darker skinned individuals than NB-UVB (shorter treatment times), but largely has been replaced by NB-UVB
- **Excimer laser** – 308 nm; high-intensity treatment with higher efficacy than standard NB-UVB for treating smaller surface areas (<2 cm<sup>2</sup>; e.g., in psoriasis and vitiligo)

## Extracorporeal photochemotherapy

- Pheresis via venous catheter in arm vein → blood cells separated into leukocyte-rich buffy coat and RBCs (returned back to patient) → 8-methoxypsoralen added to leukocytes → UVA radiation → reinfusion (net gain of 500 mL of fluid, but initially 200–400 mL are pheresed) (Fig. 2-1)
  - Usually 2-day cycle every 4 weeks and slow weaning after desired response
- Various effects on immune system, including T-cells (e.g., apoptosis of activated T-cells, induction of regulatory T-cells/immunologic tolerance), cytokines (e.g., favors immunoregulatory cytokines), and dendritic cells (↓#)
- Effective in CTCL (selectively targets lymphoma cells; can be used in combination with other treatments) and other dermatoses (e.g., scleroderma, **chronic GVHD**, nephrogenic systemic fibrosis, and pemphigus)
- **Contraindicated in severe cardiac disease** (because of difficulty in handling added fluid volume); caution in patients with low BP, hematocrit, and CHF
- SEs: nausea, photosensitivity, hypotension, CHF, and tachycardia





**Figure 2-1.** Extracorporeal photochemotherapy. Blood is accessed via a 16-gauge needle in a peripheral vein, heparinized, and collected by the ECP unit. UVADEX (8-methoxy-psoralen; 8-MOP) is automatically injected into the ECP unit at an appropriate dose. The patient undergoes discontinuous pheresis cycles to separate out the leukocyte-rich buffy coat, which is eventually fed through a one-cell-thick transparent cassette for exposure to UVA light in the presence of 8-MOP. These photochemically altered cells are then reinfused, as are the previously separated red blood cells and plasma. The entire procedure takes approximately 3 hours. The treatment is typically repeated a second day, and this 2-day cycle is typically repeated monthly. (Reprinted from Feldman, Steven R., Levender, Michelle M., Adherence to drug therapy. In: Wolverson, Steven E. *Comprehensive Dermatologic Drug Therapy*, 3rd ed. Edinburgh: Elsevier Saunders; 2007. p. 292 Fig. 23-1)

## Photodynamic therapy (PDT)

- Activation of topical photosensitizer by light
  - **Aminolevulinic acid (ALA):** activated by **blue light** (Blu-U device); no need for occlusion
  - **Methyl aminolevulinate (MAL):** activated by **red light** (Aktilite) and is more lipophilic; **occlusion recommended**
    - Mnemonic: "Red = Evil = Mal (Spanish for evil)"
  - These photosensitizers are ultimately converted to **protoporphyrin IX** within cells → activated to a higher energy state (along with production of reactive oxygen species, including singlet  $O_2$ ) primarily with light  $\approx 410$  nm (Soret band, blue), but also has other peaks (e.g., 635 nm, red) → localize by mitochondria → necrosis/apoptosis of malignant cells
    - **Neoplastic cells accumulate more porphyrins than normal cells** – thus PDT effective in actinic keratoses and nonmelanoma skin cancers
    - Of note, **protoporphyrin IX** is also elevated in the inherited condition, **protoporphyrria**
    - In acne, targets sebaceous glands and *P. acnes*, which accumulates porphyrins (light alone is effective in acne +/- photosensitizer)
  - Only FDA approved indication is actinic keratosis ( $\approx 90\%$  response on individual lesions), but also used in BCC, SCCIS, acne, photoaging, hidradenitis, and MF
  - Technique: 1) skin cleansed (acetone for ALA and gentle curette debridement of scale/crust for MAL), 2) photosensitizer applied, 3) incubation time (3–4 hours for MAL, 1–4 hours for ALA usually), 4) light exposure (37 J/cm<sup>2</sup> for MAL – 7–9 mins, 10 J/cm<sup>2</sup> for ALA – 16 mins), and 5) retreat in 7 days for MAL and 1 to 2 months for ALA if needed

- Protective eyewear during procedure and avoid sunlight for 48 hours
- Pregnancy category C and unknown lactation potential
- SEs: phototoxic reactions/photosensitivity, hypo-/hyperpigmentation, hypersensitivity to photosensitizer, pain, systemic absorption, and inflammation (edema, blistering, and crusting)

## 2.8 MISCELLANEOUS AGENTS

### Sunscreens (Box 2-2)

- SPF = MED of protected skin divided by MED of unprotected skin; SPF  $\geq 15$  or 30 recommended
- Broad-spectrum = UVA + UVB protection
- Water resistant = maintenance of SPF after 40 or 80 minutes in water
- **Chemical absorbers:** aromatic compounds that **absorb** radiation and convert it into longer, lower-energy wavelengths
  - Some are more targeted against UVB (e.g., octinoxate, PABA, cinnamates, octyloctylene, and padimate O); whereas others favor UVA spectrum (e.g., oxybenzone, avobenzone, and ecamsule)
- **Physical blockers:** chemically inert compounds that **reflect/scatter** radiation
  - Zinc oxide and titanium dioxide
  - More broad-spectrum coverage (UVA, UVB, and visible light) → better for patients with photosensitivity disorders
  - Do not generally cause contact dermatitis

**Box 2-2. Common Sunscreen Components**

**UVB blockers**

Octinoxate (octyl methoxycinnamate)  
Octisalate (octyl salicylate)  
Octocrylene  
Ensulizole (phenylbenzimidazole sulfonic acid)

**UVA blockers**

Oxybenzone  
Meradimate (methyl anthranilate)  
Avobenzone (Parsol 1789)  
Ecamsule (Mexoryl SX)

**Physical blockers**

Titanium dioxide  
Zinc oxide

(Reprinted from Levy, Stanley B., *Sunscreens*. In: Wolverton, Steven E. *Comprehensive Dermatologic Drug Therapy*, 3rd ed. Edinburgh: Elsevier Saunders; 2007. p552, Box 46-1)

- SEs: irritation, contact urticaria, irritant contact dermatitis, **allergic and photo-allergic contact dermatitis** (oxybenzone is #1 culprit; cinnamates and PABA also common), photosensitivity, and may ↓vitamin D synthesis (can supplement)
- Dihydroxyacetone (found in sunless tanning products) has only SPF 3 to 4 protection

## Topical cosmetic agents

### Eflornithine

- Binds/inhibits **ornithine decarboxylase**; used in treatment of female facial hirsutism; acne is most common SE

### Hydroquinone

- Lightens skin color via active reduction of pigment production (i.e., auto-oxidation of melanin, tyrosinase, and phenol oxidases into various reactive substances); **competes with tyrosine as substrate for tyrosinase**; production of ROS → melanocyte damage
  - Dermatitis is most common SE and most concerning SEs are **paradoxical hyperpigmentation** or **exogenous ochronosis** (usually at higher concentrations for longer time periods)
  - Other bleaching agents: monobenzyl ether of hydroquinone (potent; used for permanent depigmentation of normal skin in severe vitiligo) and mequinol

### Bimatoprost

- **Prostaglandin analog** that is approved for eyelash hypotrichosis (↑length, thickness, and pigment); SEs include periorbital skin pigmentation, **iris hyperpigmentation** (more so with glaucoma treatment than treatment of thin eyelashes), and ocular irritation

## Topical calcineurin inhibitors (TCIs)

### Pimecrolimus and tacrolimus

- MoA: **bind to FK506-binding protein** forming a complex → complex binds to enzyme calcineurin → prevention of calcineurin from dephosphorylating transcription factor NFAT-1 → ↓transcription of cytokine IL-2 → ↓T-cell activation/proliferation
- Dermatologic uses: atopic dermatitis (FDA approved), lichen planus, vitiligo, psoriasis, cutaneous lupus, and Zoon's balanitis
- SEs: **black box warning for malignancy** (likely extremely low, if any, true risk); be aware of **high levels of absorption in Netherton syndrome**; burning sensation with initial use of tacrolimus

## Psychiatric agents

- For a proper discussion of the subject, we recommend reading Chapter 31 of *Comprehensive Dermatologic Drug Therapy* by Wolverton
- Some classic uses in dermatology include:
  - Doxepin for depressed patients with neurotic excoriations
  - Pimozide (low doses of 3–5 mg/day) for **delusions of parasitosis**
    - Antipsychotic (potent centrally acting dopamine receptor antagonist)
    - SEs include: **extrapyramidal adverse effects** (tardive dyskinesia – may be irreversible with long-term use, withdrawal dyskinesia, and akathisia), and cardiac effects (e.g., **arrhythmias** from a **prolonged QT interval**) – not typically seen with low doses
  - Atypical antipsychotics (e.g., risperidone, olanzapine, and quetiapine) for delusions of parasitosis
    - Dopamine (D2) and serotonin receptor antagonists
    - Significantly ↓risk of extrapyramidal adverse effects (vs pimozide)
  - Amitriptyline for nonspecific cutaneous sensations, such as burning/stinging/pain
    - Works as analgesic in this scenario
    - SEs are anticholinergic, cardiac, sedative, and orthostatic hypotension (use low doses)

## IVIG

- Comes from purified plasma of more than 1000 donors; contains supraphysiologic IgG primarily
- MoA:
  - ↓antibody production
  - ↓complement activation
  - Neutralization of pathogenic antibodies and bacterial superantigens
  - Binds various immune receptors → immunomodulation
  - ↓TNF-α and other proinflammatory cytokines
  - Antioxidant
  - Blocks Fc receptors
  - ↓T-cell activation through various pathways
  - ↑regulatory T-cells



- Contains anti-Fas receptor antibodies → ↓keratinocyte apoptosis
- ↓migration of immune cells to target tissues
- Dose: varies, but generally 1 cycle = 2 g/kg total, divided into 3 doses, with 1 dose given on each of the 3 consecutive days; usually spaced 2 to 4 weeks apart until clinical remission, then ↑intervals thereafter
- Dermatologic uses: autoimmune blistering disorders, **dermatomyositis**, **SJS/TEN** (high-dose IVIG), **Kawasaki disease**, SLE, chronic autoimmune urticaria, scleroderma, and livedoid vasculopathy
- SEs: **infusion-related adverse effects** (e.g., headache, myalgia, flushing, fever, and wheezing; pretreatment with antihistamines/NSAIDs/corticosteroids may help), **fluid overload** (i.e., in cardiac failure and renal failure patients), **aseptic meningitis**, thromboembolic events (e.g., MI and stroke; as a result of ↑serum viscosity), and dyshidrotic hand eczema
  - Screen for immunoglobulin levels before treatment – patients with IgA deficiency may develop **anaphylaxis with treatment**
  - Patients with ↑rheumatoid factor and/or cryoglobulins have ↑risk of renal failure with treatment

## Antiandrogens and androgen inhibitors

### Spironolactone

- MoA: **antiandrogen; blocks androgen receptor** → ↓androgen production; aldosterone antagonist = diuretic properties
- Dermatologic uses: hirsutism, acne (at lower doses), and androgenetic alopecia
- SEs: **hyperkalemia** (typically in patients with renal insufficiency; do not give with agents that ↑K+), **gynecomastia**, agranulocytosis (rare), and estrogen-dependent malignancies (debatable)
- **Category X in pregnancy** → feminizes male fetuses

### Finasteride and Dutasteride

- MoA: finasteride is **type II 5-α reductase inhibitor** (of note, 5-α reductase converts testosterone to dihydrotestosterone [DHT]) and dutasteride inhibits **type I and II 5-α reductase**
- Dermatologic uses: androgenetic alopecia (**dutasteride may be more effective** than finasteride based on a recent head-to-head study), hirsutism, and hidradenitis suppurativa
- SEs: **sexual** (↓libido, impotence, and abnormal ejaculation), gynecomastia, ↓overall risk of prostate cancer, and a possible slight ↑**high-grade prostate cancer** and breast cancer; **teratogenic** (if pregnant female is exposed)
  - A recent, large random, controlled trial found: ↓overall risk of prostate cancer, ↓low-grade prostate cancer, and slight ↑high-grade prostate cancer (3.5% vs 3.0%; RR = 1.17); no difference in mortality between the finasteride and placebo groups

## Vitamin D<sub>3</sub> analogs

### Calcipotriene and calcitriol

- MoA: product binds to vitamin D receptors → drug-receptor complex + RXR-α binds to DNA at vitamin D response elements → ↓keratinocyte proliferation/epidermal differentiation, ↓IL-2/IL-6/IFN-γ/GM-CSF, ↓NK-cell and cytotoxic T-cell activity, ↑involucrin/transglutaminase → enhanced cornified envelope formation
- Dermatologic uses: primarily psoriasis, but also morphea, vitiligo, and prurigo nodularis
- SEs: **hypercalcemia** (uncommon), irritation (most common), and mild photosensitivity

## Attenuated androgens

### Danazol and stanozolol

- MoA: complex, but involves ↑ production of various proteins by the liver, including various clotting factors, inhibitor of first component of complement (C1 INH), fibrinolytic proteins
- Dermatologic uses: **hereditary angioedema** (FDA approved), cryofibrinogenemia, **lipodermatosclerosis**, and livedoid vasculitis
- SEs: **hormonal-related SEs** (hirsutism, deeper voice, alopecia, acne, and menstrual irregularities), muscle cramps, **myalgias**, **myopathy** (in patients on statins), hematuria/hemorrhagic cystitis, insulin resistance, headaches, worsening HTN and CHF (drugs retain sodium), hyperlipidemia, and hepatic SEs (jaundice and liver tumors)
- Do NOT use in childhood or pregnancy

## Agents used for antiinflammatory properties

### Clofazimine

- Riminophenazine dye used for **antibiotic** (i.e., antimycobacterial, especially multibacillary leprosy and erythema nodosum leprosum) and **antiinflammatory** (e.g., SLE, pyoderma gangrenosum, **erythema dyschromicum perstans**, and discoid LE) purposes
- SEs: reversible **orange-brown skin and body fluid** discoloration, xerosis, and crystal deposition in organs → enteropathy/splenic infarction/eosinophilic enteritis/cardiac dysrhythmia

### Colchicine

- MoA: **binds tubulin dimers** in leukocytes → mitotic arrest in metaphase and ↓chemotaxis
- Dermatologic uses: familial mediterranean fever (treatment of choice), neutrophilic dermatoses (e.g., Behcet's disease), cutaneous small vessel vasculitis, autoimmune connective tissue disorders, and gout
- SEs: GI SEs (e.g., **cramping**, **diarrhea**, and abdominal pain, which can → discontinuation); rarely **bone marrow suppression**, **neuropathy**, and myopathy

### Nicotinamide (vitamin B<sub>3</sub>)

- MoA: inhibits PARP-1 → ↓NFκB transcription → ↓leukocyte chemotaxis; ↓lysosomal enzyme release; stabilizes leukocytes by inhibiting PDE → immunomodulation; ↓lymphocytic transformation/antibody production; ↓mast cell degranulation
- Dermatologic uses: **pellagra**, **autoimmune bullous disorders** (in combination w/ TCN), **NMSC chemoprevention** (2015 NEJM study showed 23% reduction in new skin cancers compared to placebo, with no increase in adverse side effects)
- SEs: very safe – occasional GI complaints, **flushing** and headaches

### Potassium iodide

- MoA: unknown, likely antiinflammatory (especially toward neutrophils)
- Dermatologic uses: **sporotrichosis**, **erythema nodosum**, and **erythema induratum**
- SEs: **hypothyroidism** (with chronic high-dose treatment, mainly in patients with preexisting thyroid issues), chronic iodine intoxication, skin eruptions (e.g., **iododerma**, acneiform, dermatitic, and vascular), GI SEs (most common), “iodism” (metallic taste, sore/burning mouth, and headache), and **exacerbation of dermatitis herpetiformis**
- Check for thyroid disorders before starting medication; do not give large doses during pregnancy (can → goiter/hypothyroidism in fetus)
- Pregnancy category D

### Thalidomide

- MoA:
  - CNS effects of sedation
  - Antiinflammatory effects: **inhibits TNF-α** and IFN-γ, ↓IL-12 production, ↓helper T-cells, ↑suppressor T-cells, ↑IL-4/5 production, ↓PML chemotaxis, and ↓histamine/acetylcholine/prostaglandins
  - Neural effects – helpful in **prurigo nodularis**
  - Vascular effects (i.e., inhibits angiogenesis) – helpful in Kaposi sarcoma
- Dermatologic uses: **erythema nodosum leprosum** (FDA approved), HIV-related disorders, **lupus erythematosus**, GVHD, prurigo nodularis, and neutrophilic dermatoses (e.g., Behcet’s disease)
- SEs: **teratogenic** (category X – most common defect is **phocomelia**), peripheral **neuropathy** (proximal muscle weakness + distal painful paresthesias/sensory loss), **venous thrombosis**, hypersensitivity reaction (more common in HIV patients), **sedation/drowsiness** (**most common**), constipation, and various drug interactions
- Medication is regulated in the United States by the STEPS program, involving laboratory monitoring, neurologic monitoring, and pregnancy monitoring (pregnancy category X)

### Pentoxifylline

- Phosphodiesterase inhibitor that:
  - ↑erythrocyte/leukocyte deformability
  - ↓platelet aggregation

- ↓TNF-α
- ↓neutrophil adhesion
- Used in Raynaud’s, **livedoid vasculopathy**, necrobiosis lipoidica, venous ulcers, and lipodermatosclerosis
- SEs are primarily gastrointestinal; decrease dose in renal dysfunction

## Agents for hyperhidrosis

### Glycopyrrolate

- Anticholinergic agent used orally or topically for hyperhidrosis
- MoA: blocks acetylcholine’s effects on sweat glands
- SEs include **anticholinergic effects** (e.g., dry mouth and blurred vision), seizures (rare), and hyperthermia (rare)
- Caution with tricyclic antidepressants, atenolol, and digoxin

### Oxybutynin

- Anticholinergic agent
- Approved for overactive bladder but can be used for hyperhidrosis
- SEs: anticholinergic effects (eg. urinary retention, constipation) primarily

## 2.9 DRUG INTERACTIONS AND THE CYTOCHROME P-450 SYSTEM

- This is a very brief review of drug interactions, mainly as they relate to cytochrome P-450 (CYP) system

### Key points

- CYP enzymes metabolize endogenous and exogenous compounds (e.g., drugs)
- Most commonly located in **endoplasmic reticulum of hepatocytes**
- Divided into families and subfamilies based on genetic similarity
- Defects in CYP genes can → altered drug metabolism (e.g., CYP2D6 mutations may → poor tolerance to doxepin)
- Substrate drugs = drugs metabolized by a certain CYP isoform
  - If given with a drug that **inhibits** the CYP → ↓clearance of substrate drug → ↑levels of substrate drug and possible toxicity
    - In this scenario, may need ↓dose of substrate drug
  - If given with a drug that **induces** the CYP → ↑clearance of substrate drug → ↓levels of substrate drug and ↓therapeutic effect
    - In this scenario, may need ↑dose of substrate drug

### Specific CYP isoforms

#### CYP1A2

- Substrates: theophylline/caffeine, warfarin, and pimozide

- Inhibitors: **fluoroquinolones**, **macrolides** (e.g., **erythromycin**), and **ketoconazole**
- Inducers: phenytoin, barbiturates, rifampin, and cigarette smoke

### CYP2C9

- Substrates: **phenytoin**, sulfonamides, **warfarin**, fluvastatin, and losartan
- Inhibitors: **fluconazole** and TMP-SMX
- Inducers: carbamazepine and rifampin

### CYP2D6

- Accounts for  $\frac{1}{4}$  of all drug metabolism
- Substrates: tricyclic antidepressants (e.g., **doxepin** and amitriptyline), **metoprolol**/**propranolol**, antidysrhythmics (e.g., encainide and propafenone), antipsychotics (e.g., clozapine and pimozide)
- Inhibitors: **SSRIs** (e.g., fluoxetine and sertraline), pimozide, and **terbinafine**
- Inducers: carbamazepine, phenytoin, and rifampin

### CYP3A4 (most relevant to dermatologists)

- Accounts for **up to 50%** of all drug metabolism
- Substrates: many! – **warfarin**, carbamazepine, doxepin, sertraline, antidysrhythmics (e.g., amiodarone, digoxin, and quinidine), CCBs (e.g., diltiazem and **nifedipine**), chemotherapy (e.g., doxorubicin, vinblastine, and cyclophosphamide), **H1 antihistamines**, **HMG CoA reductase inhibitors** (lovastatin and simvastatin), **oral contraceptives/estrogens**, **cyclosporine**, **tacrolimus**, corticosteroids, dapsone, **pimozide**, benzodiazepines, **protease inhibitors**, and colchicine
- Inhibitors: **azole** antifungals (e.g., ketoconazole and itraconazole), **clarithromycin/erythromycin**, metronidazole, protease inhibitors, SSRIs (e.g., sertraline), **grapefruit juice**, cimetidine, and CCBs
  - Important examples: itraconazole given with cyclosporine → toxicity; same idea if itraconazole given w/ warfarin (→ ↑ anticoagulant potential/INR) or lovastatin (→ rhabdomyolysis)
  - Azithromycin is NOT a CYP3A4 or -1A2 inhibitor like other macrolides
- Inducers: **rifampin**, **griseofulvin**, **anticonvulsants** (e.g., phenytoin and carbamazepine), dexamethasone, and **St. John's wort**
  - e.g. rifampin given with oral contraceptives → failure of oral contraceptives
- Classic CYP mnemonics
  - Queen Barbara's Phenny – she refuses greasy carbs and alcohol chronically
    - Inducers: quinidine, barbiturates, phenytoin, rifampin, griseofulvin, carbamazepine, chronic alcohol intake
  - PICK EGS
    - Inhibitors: protease inhibitors, isoniazid, cimetidine, ketoconazole, erythromycin, grapefruit juice, sulfonamides

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# 3

## General Dermatology

*Ali Alikhan and Thomas Hocker*

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### 3.1 PAPULOSQUAMOUS DERMATOSES

#### Psoriasis

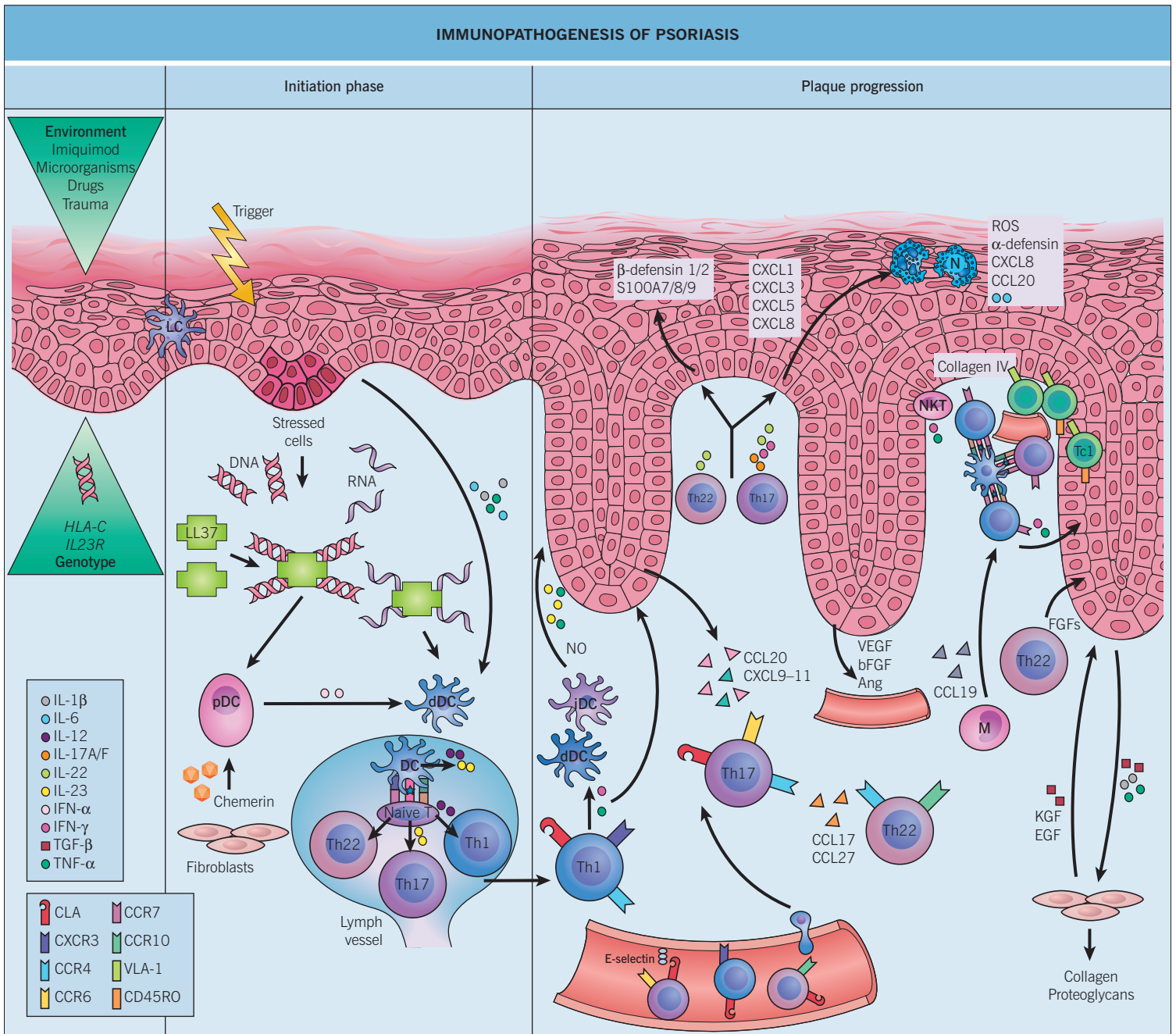
##### Epidemiology

- 2% worldwide prevalence
- Psoriatic arthritis (PsA) in 5%–30%
- Peaks at 20–30 yrs and 50–60 yrs

##### Pathogenesis (Fig. 3-1)

- Genetic factors (family history, twin studies) important

- Psoriasis susceptibility regions, PSORS1–9: **PSORS1** (chromosome 6p and contains *HLA-Cw6* allele) is **most important**
  - PSORS1 in 50% of patients
- Important HLA associations in psoriasis:
  - **HLA-Cw6 (strongest association)**: 10–15 times ↑ risk
    - Positive in **90% of early-onset psoriasis**, 50% of late onset (vs 7% of control population)
    - Strongest HLA risk factor for early-onset disease (Cw6 > B57, DR7)
    - Also strongly a/w **guttate psoriasis** (74%)
  - **HLA-B27**: sacroiliitis-associated psoriasis, PsA, and pustular psoriasis



**Figure 3-1.** Immunopathogenesis of psoriasis. The occurrence of triggering environmental factors in genetically predisposed individuals, carrying susceptibility alleles of psoriasis-associated genes, results in disease development. During the initiation phase, stressed keratinocytes can release self DNA and RNA, which form complexes with the cathelicidin LL37 that then induce interferon-α (IFN-α) production by plasmacytoid dendritic cells (pDCs; recruited into the skin via fibroblast-released chemerin), thereby activating dermal DCs (dDCs). Keratinocyte-derived interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) also contribute to the activation of dDCs. Activated dDCs then migrate to the skin-draining lymph nodes to present an as-yet-unknown antigen (either of self or of microbial origin) to naive T-cells and (via secretion of different types of cytokines by DCs) promote their differentiation into T helper 1 (Th1), Th17, and Th22 cells. Th1 cells (expressing cutaneous lymphocyte antigen (CLA), CXCR3, and CCR4), Th17 cells (expressing CLA, CCR4, and CCR6), and Th22 cells (expressing CCR4 and CCR10) migrate via lymphatic and blood vessels into psoriatic dermis, attracted by the keratinocyte-derived chemokines CCL20, CXCL9-11, and CCL17; this ultimately leads to the formation of a psoriatic plaques. Th1 cells release IFN-γ and TNF-α, which amplify the inflammatory cascade, acting on keratinocytes and dDCs. Th17 cells secrete IL-17A and IL-17F (and also IFN-γ and IL-22) which stimulate keratinocyte proliferation and the release of β-defensin 1/2, S100A7/8/9, and the neutrophil-recruiting chemokines CXCL1, CXCL3, CXCL5, and CXCL8. Neutrophils (N) infiltrate the stratum corneum and produce reactive oxygen species (ROS) and α-defensin with antimicrobial activity, as well as CXCL8, IL-6, and CCL20. Th22 cells secrete IL-22, which induces further release of keratinocyte-derived T-cell-recruiting chemokines. Moreover inflammatory DCs (iDCs) produce IL-23, nitric oxide (NO) radicals, and TNF-α, whereas natural killer T-cells (NKT) release TNF-α and IFN-γ. Keratinocytes also release endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietin (Ang), thereby promoting neoangiogenesis. Macrophage (M)-derived chemokine CCL19 promotes clustering of Th cells expressing chemokine receptor CCR7 with DCs in the proximity of blood vessels and further T-cell activation. At the dermal-epidermal junction, memory CD8+ cytotoxic T-cells (Tc1) expressing very-late antigen-1 (VLA-1) bind to collagen IV, allowing entry into the epidermis and contributing to disease pathogenesis by releasing both Th1 and Th17 cytokines. Cross-talk between keratinocytes producing TNF-α, IL-1β, and transforming growth factor-β (TGF-β) and fibroblasts, which in turn release keratinocyte growth factor (KGF), epidermal growth factor (EGF), and TGF-β. Th22 cells releasing FGFs possibly contribute to tissue reorganization and deposition of the extracellular matrix (e.g., collagen, proteoglycans). LC, Langerhans cell Courtesy, Dr Paola DiMeglio. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- **HLA-B13 and HLA-B17:** guttate and erythrodermic psoriasis
  - **HLA-B8, Bw35, Cw7, and DR3:** palmoplantar pustulosis
  - **Immunologic factors:**
    - T-cell disorder, primarily: CD8+ in epidermis and mix of CD4+/CD8+ in dermis
      - Primarily memory T-cells with CLA and chemokine receptors (e.g., CCR4); also some NK T-cell involvement
      - Increased: Th1 cytokines (e.g., IFN $\gamma$  and IL-2), IL-1, IL-6, and TNF- $\alpha$
      - Decreased: IL-10
      - **IL-23 (from DCs)  $\rightarrow$  Th17 cell stimulation  $\rightarrow$  IL-17 and IL-22 release  $\rightarrow$  dermal inflammation and keratinocyte replication**
    - $\uparrow$  dendritic cells in psoriatic skin
    - $\uparrow$  CXCL8  $\rightarrow$  neutrophil chemotaxis (spongiform pustules of Kogoj and microabscess of Munro)
    - VEGF  $\rightarrow$  angiogenesis
    - Keratinocytes secrete **antimicrobial proteins** (hBD1-2, cathelicidin LL37, and SLP1), IL-1, IL-6, IL-8, and TNF- $\alpha$ ; also express TLRs
    - STAT-3 expression  $\rightarrow$  keratinocyte proliferation
  - **Triggering factors:**
    - **External:** trauma (**Koebner phenomenon**) – 2 to 6 week lag time
    - **Systemic:** infections (**streptococcal pharyngitis #1**), HIV, endocrine factors (e.g., **hypocalcemia** in generalized pustular psoriasis and **pregnancy** in impetigo herpetiformis), stress, **drugs** (lithium, IFNs,  **$\beta$ -blockers**, antimalarials, **TNF- $\alpha$  inhibitors**, and **CS tapers** in pustular psoriasis), alcohol consumption, smoking, and obesity
      - Latency period between drug initiation and skin eruption varies:
        - ◆ Short latency (<4 weeks): terbinafine, NSAIDs
        - ◆ Intermediate latency (4 to 12 weeks): antimalarials, ACE inhibitors
        - ◆ Long latency (>12 weeks):  $\beta$ -blockers, lithium
      - **TNF- $\alpha$  inhibitors** may  $\rightarrow$  plaque psoriasis and/or palmoplantar pustulosis
- Clinical features**
- **Chronic plaque psoriasis** (most common)
    - Symmetric, well defined red papules and plaques w/ prominent white scale
    - Most common sites: scalp, elbows, knees, presacrum, hands, feet, and genitalia
  - **Guttate psoriasis:** children and adolescents; drop-like lesions measuring 2–6 mm; symmetric distribution; favors trunk and proximal extremities
    - Triggers: **group A Strep infection (oropharynx or perianal)** or URI (1–3 weeks prior to onset)
    - 40% progress to plaque-type
  - **Erythrodermic psoriasis:** generalized erythema and scale (>90% BSA)
    - Triggers: poor management decisions most common (e.g., abrupt withdrawal of systemic steroids)
  - **Generalized pustular psoriasis:**
    - **Impetigo herpetiformis:** pregnancy-associated; begins in flexures then generalizes w/ toxicity; early delivery recommended
    - von Zumbusch: rapid and generalized, painful skin, fever, **leukocytosis**, **hypoalbuminemia**, and malaise; a/w **hypocalcemia** (risk factor)
  - **Palmoplantar pustulosis:** pustules and yellow-brown macules localized to palms/soles; has a chronic course
    - May be a/w sterile inflammatory bone lesions (**SAPHO syndrome**)
  - **Acrodermatitis continua of Hallopeau:** “lakes of pus” on distal fingers, toes, and nail beds  $\rightarrow$  scale, crust, and **nail shedding**
  - **Site-specific types**
    - Scalp: can coexist w/ seborrheic dermatitis; may advance to edge of face, retroauricular areas, and upper neck
      - Psoriasis is **#1 cause of pityriasis amiantacea**
    - Inverse: shiny pink-red, **well-defined** thin plaques w/ fissuring
      - Axillae, inguinal crease, intergluteal cleft, inframammary region, and retroauricular folds
    - Oral: annulus migrans (presents like geographic tongue, seen in pustular psoriasis)
    - Nail: **fingernails** > toenails (vs opposite pattern in onychomycosis)
      - **Proximal matrix  $\rightarrow$  pits**
      - **Distal matrix**  $\rightarrow$  leukonychia and loss of transparency; subungual hyperkeratosis
      - **Nail bed**  $\rightarrow$  **oil spots**, **Salmon patches**, splinter hemorrhages, **onycholysis**, and subungual hyperkeratosis
  - **Psoriatic arthritis (PsA):** affects up to 30% of psoriasis patients (correlated w/ skin severity); typically **RF-negative** (“seronegative”); classic early symptom = **morning joint stiffness** lasting >1hr; **vast majority have nail changes** +/- tendon/ligament involvement (**enthesopathy/enthesitis**); strong genetic predisposition (**50% HLA-B27+**); Rx: biologics, MTX, apremilast, cyclosporine, and tofacitinib
    - Five distinct PsA patterns:
      - **Oligoarthritis** w/ swelling and tenosynovitis of hands (**60%–70%**): affects **DIP + PIP** joints of hand and feet (may  $\rightarrow$  “sausage digit”) +/- large joint involvement; **sparing MCP** (vs RA)
      - Asymmetric DIP involvement + nail changes (16%): exclusively affects DIP  $\rightarrow$  “sausage digit,” nail damage
      - Rheumatoid arthritis-like (15%): symmetric polyarthritis of **small and medium** joints (PIP, MCP, wrist, ankle, and elbow); hard to DDx from RA and **may be RF+**
      - Ankylosing spondylitis (5%): axial arthritis +/- sacroiliac, knee and peripheral joint involvement; M > F, **usually HLA-B27+**, a/w IBD and uveitis
      - Arthritis mutilans (5%): least common, most severe (osteolysis of phalanges/metacarpals  $\rightarrow$  short, wide, and soft digits w/ “**telescoping phenomenon**”)

- Comorbidities
  - ↓risk of allergic diseases
  - ↓risk of superinfection (due to ↑antimicrobial peptides)
  - Possible ↑risk of lymphoma
  - ↑risk of cardiovascular diseases, HLD, HTN, DM, NASH, and metabolic syndrome
    - Systemic psoriasis treatments may ↓risk
  - Asymmetric anterior uveitis (15% of juvenile psoriasis)

### Histopathology

- Mature plaques:
  - **Confluent parakeratosis**
  - **Regular acanthosis** w/ elongated rete ridges
  - Thinning of suprapapillary plates
  - ↓ or absent stratum granulosum
  - Dilated capillaries in dermal papillae
  - Micropustules of **Kogoj** (stratum spinosum) and microabscesses of **Munro** (stratum corneum)
    - Mnemonic: "Marilyn Munro is always on top (higher in epidermis)"
- Guttate:
  - Milder acanthosis, spongiosis, foci of intraepidermal neutrophils, **mounded parakeratosis**, ↓granular layer
  - Thin, tortuous capillaries in papillary dermis
  - Mixed perivascular infiltrate w/ scattered neutrophils
- Pustular:
  - Large clusters of neutrophils in upper epidermis

### Treatment

- Topical treatments – may be used alone for mild psoriasis
  - **Corticosteroids**: first line for mild-moderate psoriasis
  - Anthralin: second line
  - Vitamin D3 analogs: typically used in conjunction w/ topical corticosteroids
  - Topical retinoids: tazarotene
  - Miscellaneous: salicylic acid, coal tar, and topical calcineurin inhibitors (especially facial and flexural)
- **Phototherapy**: first line in moderate to severe psoriasis
  - NB-UVB (311–313 nm): highly effective, ↓risk of secondary NMSCs relative to BB-UVB and PUVA
  - BB-UVB: more effective than NB-UVB for **guttate psoriasis flares**
  - Excimer laser (308 nm): useful for limited/localized disease
  - PUVA: topical for limited areas; oral for more generalized disease
  - Goeckermann regimen: combination of crude coal tar and BB-UVB
- **Systemic therapy**: moderate-severe psoriasis
  - Apremilast (PDE-4 inhibitor), tofacitinib (JAK 1/3 inhibitor) = newest oral agents for psoriasis
  - Methotrexate (MTX)
  - Cyclosporine: **do not use >1yr**; ↑risk SCCs (particularly in a/w PUVA)
  - Systemic retinoids: acitretin is the only systemic retinoid used in psoriasis; **monotherapy effective in erythrodermic and pustular psoriasis**; combination

w/ phototherapy (Re-PUVA) effective for plaque psoriasis

- Biologics
  - TNF- $\alpha$  inhibitors: infliximab, etanercept, and adalimumab
  - **IL-12 and IL-23 inhibitor**: ustekinumab
  - **IL-17 inhibitors**: secukinumab (FDA approved in 2015), brodalimumab, and ixekizumab (FDA approved in 2016)

### Prognosis/clinical course

- Depends on the type; often chronic
- Spontaneous remission in  $\leq 35\%$

### Additional boards factoids

- **Woronoff ring**: pale blanching ring around psoriatic lesions
- **Auspitz sign**: scraping of psoriasis scale → pinpoint bleeding (due to dilated capillaries and suprapapillary plate thinning)
- ToC for psoriasis subtypes:
  - Pustular (von Zumbusch): **acitretin** (>cyclosporine, MTX, and biologics)
  - Impetigo herpetiformis: **early delivery**, prednisone
  - Guttate: **BB-UVB** at erythemogenic doses (>NB-UVB)
  - Erythrodermic: cyclosporine, infliximab, and acitretin

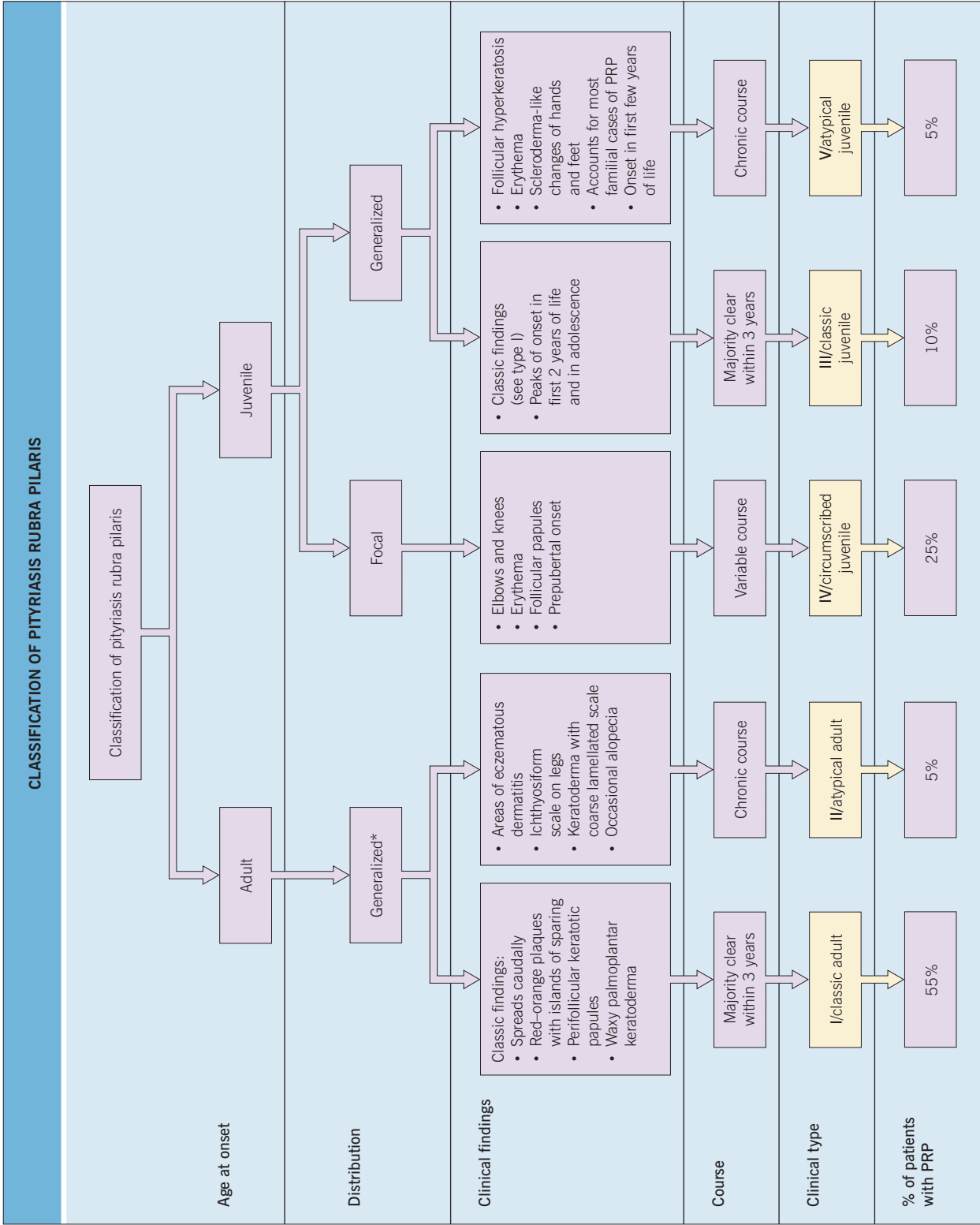
## Pityriasis rubra pilaris (PRP)

### Pathogenesis/epidemiology

- Bimodal age distribution: first and sixth decade
- Unknown etiology

### Clinical features

- Classically begins on head/neck → progresses caudally
- Most important features:
  - **Scalp erythema** w/ fine, diffuse scaling
  - Folliculocentric keratotic papules on erythematous base ("**nutmeg-grater**" papules)
    - Papules coalesce into **orange to salmon-colored** plaques w/ "**islands of sparing**" on trunk and extremities → can progress to erythroderma w/ exfoliation
  - **Orange-red waxy keratoderma** of palms/soles ("**sandal-like PPK**") w/ fissures
  - Thick, yellow-brown nails w/ subungual debris; **lacks nail pits (vs Pso)!**
- **Five distinct subtypes (Fig. 3-2)** and a sixth newer subtype (generalized PRP in HIV patients w/ hidradenitis suppurativa, acne conglobata, and elongated follicular spines); **all except type 4 are generalized**
  - **Type 1** (55%, classic adult): **most common form**, rapid onset of classic PRP features, good prognosis (80% resolve within 3 yrs)
  - **Type 2** (5%, atypical adult): slow onset, **ichthyosiform leg lesions + keratoderma w/ coarse and lamellated scale +/- alopecia**; chronic course
  - **Type 3** (10%, classic juvenile): same presentation/course as type 1; peaks in adolescence and first 2 yrs of life
  - **Type 4** (25%, circumscribed juvenile): **most common form in children (Fig. 3-3)**; only **localized** form of



**Figure 3-2.** Classification of pityriasis rubra pilaris (PRP). \*A generalized distribution of PRP, often with findings similar to type I, may be seen in association with elongated follicular spines, acne conglobate, and hidradenitis suppurativa in HIV-infected individuals; this is referred to as type VI PRP or HIV-associated follicular syndrome. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)





**Figure 3-3.** Circumscribed juvenile (type IV) PRP. PRP, pityriasis rubra pilaris (From Schachner LA, Hansen RC. *Pediatric Dermatology*, 4th ed. Elsevier. 2011.)

PRP; p/w follicular papules and erythema on elbows and knees; prepubertal onset; variable course

- Type 5 (5%, atypical juvenile): first few years of life, PRP + sclerodermoid changes of hands/feet; chronic

#### Histopathology

- Alternating vertical and horizontal orthohyper- and parakeratosis (“checkerboard pattern”)
- **Follicular plugging**
- **“Shoulder parakeratosis”** (parakeratosis at edges of hair follicle orifice)
- Irregular acanthosis w/ thickened suprapapillary plates (vs Pso)
- Focal acantholysis or acantholytic dyskeratosis (recently-appreciated findings)

#### Treatment

- First line: isotretinoin or **acitretin**
- Others: high-dose vitamin A, MTX, TNF- $\alpha$  inhibitors, phototherapy

#### Prognosis/clinical course

- Classic forms (type 1 and 3) reliably self-resolve in 3–5 yrs
- Atypical and circumscribed forms (types 2, 4, and 5) persist much longer

#### Additional boards factoids

- Phototherapy may induce flares → phototesting recommended

### Seborrheic dermatitis

#### Epidemiology/pathogenesis

- Peak in fourth to sixth decades, but occurs in all ages; M > F

- Multifactorial etiology
  - $\uparrow$ *Malassezia furfur* in cutaneous lesions
  - Sebum composition altered ( $\uparrow$ triglycerides/cholesterol;  $\downarrow$ squalene and FFA)
  - Immune dysregulation (some cases)

#### Clinical features

- Pediatric:
  - Erythematous, scaly, sometimes pruritic rash affecting “seborrheic” areas (scalp, face, postauricular, presternal, and intertriginous areas)
  - Infants often present w/ “**cradle cap**” (greasy yellow scales adherent to scalp)
  - Erythematous, scaly, macerated plaques in body creases (anterior neck crease, axillae, groin, and popliteal fossae)
- Adolescent/adult:
  - Well-defined, pink-yellow patches w/ “**greasy**” scale in highly sebaceous areas (scalp, eyebrows, nasolabial folds, forehead, ears/retroauricular, central chest, and intertriginous areas)
  - Often itchy (particularly scalp)
  - Dandruff (pityriasis simplex capillitii) – mild form on scalp

#### Histopathology

- Irregular to psoriasiform acanthosis, **spongiosis**, “**shoulder parakeratosis**,” superficial perivascular/perifollicular lymphocytic infiltrate

#### Treatment

- **Gold standard = topical azoles**
- Other options: ciclopirox, topical CS, TCIs, pyridione zinc, selenium sulfide, salicylic acid, and coal tar shampoos
- “Cradle cap:” frequent shampooing (antiseborrheic shampoos), baby or mineral oil, brushing/combing, and low potency topical CS

#### Prognosis/clinical course

- Infants: spontaneous resolution by 8–12 months
- Adolescents: tends to be more chronic
- Adults: chronic and relapsing

#### Additional boards factoids

- $\uparrow$ incidence and severity in **HIV** and **Parkinson’s**

### Pityriasis rosea (PR)

#### Epidemiology

- Female predominance; **10–35 yo**
- Peaks in spring and fall

#### Pathogenesis

- Possibly viral (HHV-7 and HHV-6)
- Drug-induced PR: **ACE inhibitors** (most common), NSAIDs, **gold**, bismuth,  **$\beta$ -blockers**, barbiturates, isotretinoin, metronidazole, and clonidine

#### Clinical features

- Begins w/ “**herald patch**” = solitary pink, enlarging plaque w/ fine central scale and larger **trailing collarette** of scale; favors trunk



- Diffuse eruption (begins hours to weeks later): oval patches/plaques on trunk and proximal extremities
  - Lesions appear similar to “herald patch,” but smaller
  - Vertical axes oriented along Langer’s lines (“**Christmas tree pattern**”)
  - 25% experience significant pruritus
- Atypical pityriasis rosea: term utilized when rash has unusual features, including:
  - Inverse PR pattern: prominent involvement of **intertriginous** sites, or more prominent involvement of **limbs** (> trunk)
  - Papular, vesicular, or targetoid morphology
    - PR is often more papular and extensive in African American children
  - Oral involvement (e.g., ulceration)
- Drug-induced PR-like eruptions: ↑inflammation/pruritus, lacks herald patch; older patient population

### Histopathology

- **Non-adherent thin mounds of parakeratosis** (vs thicker, adherent mounds in guttate psoriasis), **spongiosis**, perivascular lymphohistiocytic infiltrate, and **RBC extravasation**

### Treatment

- Not required; symptomatic treatment w/ topical CS, antipruritic lotions
- **Oral erythromycin** hastens clearance

### Prognosis/Clinical course

- Self-limited (6–8 weeks)
- Drug induced PR-like eruptions resolve rapidly (<2 weeks) after discontinuing drug

## Intertriginous/axillary granular parakeratosis

- **Adult women** > infants (diaper area)
- Pruritic, keratotic red-brown papules and plaques in intertriginous areas (**axillae** > **inguinal**, **inframammary**)
- Possible defect in filaggrin metabolism → retention of keratohyaline granules in SC
  - Alternative theories: irritant dermatitis, reaction to deodorants/antiperspirants
- Histology: characteristic thickened eosinophilic stratum corneum w/ prominent **parakeratosis and retained keratohyalin granules**; vascular ectasia (**Fig. 3-4**)
- Can be chronic/recurrent
- Rx: topical (corticosteroids, vitamin D analogues, keratolytics, and antifungals), destructive (cryotherapy), and systemic (isotretinoin, antifungals)

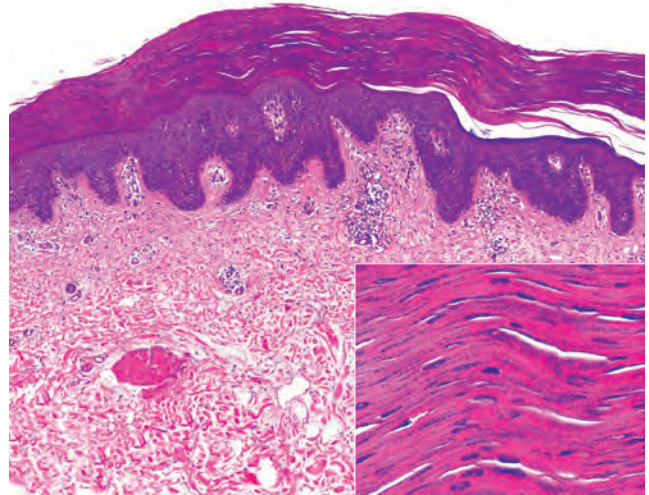
## Erythroderma

### Epidemiology

- M > F, average age =50 yo

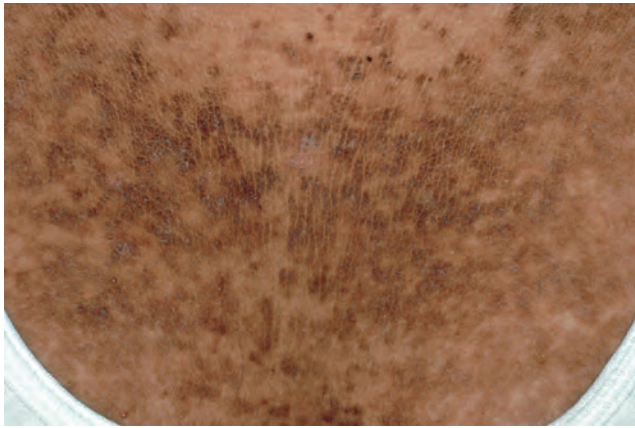
### Clinical features

- Erythema and scale involving >90% of BSA



**Figure 3-4.** Axillary granular parakeratosis. Marked, compact parakeratosis with small bluish granules within the stratum corneum representing keratohyaline granules (insert). Courtesy, Luis Requena, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Not a defined entity, but rather a clinical presentation of various disorders, characterized by:
  - **Pruritus** (>90% of cases, especially atopic dermatitis or Sezary); lichenification (>30%); dyspigmentation (>50%); PPK (30%); nail changes (40%, typically “shiny nails”)
  - Other skin findings: *S. aureus* colonization, eruptive SKs, ectropion, and conjunctivitis
  - Systemic findings: **peripheral lymphadenopathy** (#1 extracutaneous finding), hepatomegaly (20%), pedal/pretibial edema (50%), tachycardia (40%), thermoregulatory disturbances (hyperthermia > hypothermia), hypermetabolism, and anemia
- Primary (erythema involves whole skin surface in days to weeks) vs secondary (generalization of localized skin disease)
- Causes:
  - **Psoriasis (most common cause in healthy patients):**
    - Usually preceded by typical plaques
    - 25% are idiopathic; less scaly than typical psoriasis lesions
    - Erythroderma is usually **due to drug withdrawal** (steroid, MTX, or CSA)
    - Nails w/ characteristic psoriasis findings
    - Histologically, changes of early psoriasis seen
  - Atopic dermatitis:
    - Typically have atopic history
    - Severe pruritus and lichenification
    - ↑serum IgE and eosinophilia
  - **Drug reactions:**
    - **Most common cause in HIV patients** (40% vs 23% in non-HIV patients)
    - Lesions may become purpuric in ankles and feet
    - Shorter duration than other erythrodermas (resolves 2 to 6 weeks after drug withdrawal)
    - Most common drugs: **allopurinol**, **sulfa** (TMP-SMX, dapsone), **antiepileptics**, **INH**, **minocycline**, and **HAART**



**Figure 3-5.** Confluent and reticulated papillomatosis (CARP). Multiple hyperpigmented papules that are confluent centrally and assume a reticulated pattern laterally. Courtesy, Julie V Schaffer, MD. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- **Idiopathic erythroderma: elderly men w/ relapsing course**
  - Lymphadenopathy, PPK, and peripheral edema seen frequently
- CTCL (Sezary and erythrodermic MF):
  - **Sezary**: primary erythroderma; T-cell clone in blood plus one of the following: 1)  $\geq 1000$  Sezary cells/ $\mu$ L; 2) CD4:CD8 ratio of  $\geq 10:1$ ; or 3)  $\uparrow$ percentage of CD4+ cells w/ abnormal phenotype (loss of CD7 or CD26)
  - **Erythrodermic MF**: secondary erythroderma; due to progression from classic MF patches/plaques
- Less common causes: PRP, GVHD, paraneoplastic erythroderma, bullous dermatoses, and ichthyoses

#### Treatment

- Initial management: nutritional assessment, fluid and electrolyte correction; prevention of hypothermia; treatment of secondary infections
- Tailor treatment to underlying condition: sedating antihistamines, topical and/or systemic steroids (caution when tapering), **wet dressings**, and emollients

### Confluent and reticulated papillomatosis (CARP)

- Starts at puberty; **F > M**; **blacks > whites**
- Unknown etiology
- Red or brown, rough, keratotic, slightly raised papules that first appear in **intermammary region**  $\rightarrow$  spreads outward and forms reticulated pattern (**Fig. 3-5**) laterally
- Histology: **acanthosis nigricans-like** (hyperkeratosis, acanthosis, and papillomatosis)
- ToC: **Minocycline 100 mg BID x 6 weeks** (effective in 50%)
- Other options: **oral retinoids, oral antibiotics, or topical antifungals**
- **Pseudoatrophoderma colli**: variant that occurs on neck; appears as vertically-oriented hyperpigmented papillomatous lesions w/ wrinkling; also responsive to minocycline

## 3.2 ECZEMATOUS DERMATOSES

### Atopic dermatitis (AD)

#### Epidemiology

- Part of **atopic triad**: AD (often first manifestation), allergic rhinitis, and asthma
- More common in **high income and urban areas** (exposure to pollutants and lack of exposure to infectious agents may trigger development of AD)
- Affects **25% of children, 3% of adults**
- Prevalence is increasing
- Subsets:
  - **Early onset (most common)**: arises by 1–2 yo, 50% have allergen-specific IgE antibodies, 60% resolve by 12 yo
  - **Late onset**: arises after puberty
  - **Senile onset**: arises after 60 yo
- Onset: 50%–60% by first year of life (often 3–6 months), 90%–95% by 5 yo

#### Pathogenesis

- Complex interaction of epidermal barrier dysfunction, immune dysregulation, and environment
- Genetic factors are important
  - Twin studies (monozygotic > dizygotic concordance) and family history (high probability that one or both parents are atopic)
  - Genes encoding epidermal proteins (e.g., FLG and SPINK)
    - **Filaggrin (FLG) mutations** cause alterations in epidermal barrier; strongly a/w AD development, especially **severe early onset AD**
    - Barrier dysfunction causes transepidermal water loss and xerosis, allowing penetration of allergens
  - $\uparrow$ transcription of genes encoding immunologic proteins (TLR2, FCER1A, and DEFB1) and cytokines (Th2 > Th1 cytokines involved in regulation of IgE (especially **IL-4, IL-5, IL-12, and IL-13**))
    - Acute AD: **Th2 predominance** w/ eosinophilia,  $\uparrow$ IgE production and  $\downarrow$ cutaneous antimicrobial peptides
    - Chronic AD: **Th1 predominance** w/  $\uparrow$ IFN- $\gamma$
- Mediators of itch
  - Histamines less important than neuropeptides, proteases, kinins, and certain cytokines

#### Clinical features

- Clinical criteria
  - Essential: pruritus
  - Plus  $\geq$  three of the following:
    - History of xerosis
    - Personal history of allergic rhinitis or asthma
    - Onset <2 yo
    - History of skin crease involvement (antecubital, popliteal, ankle, neck, and periorbital)
    - Visible flexural dermatitis
- Acute form: erythema, edema, vesicles, oozing, and crusting
- Subacute and chronic forms: lichenification, papules, nodules, and excoriations

- **Pediatric AD**
  - Infantile (birth to 6 months of age)
    - Acute presentation and clinical features
    - Favors face, scalp, and **extensor** surfaces
    - May have overlap with seborrheic dermatitis
  - Childhood (2 yo to puberty)
    - Clinical manifestations typically more chronic in nature, though acute flares may occur
    - Favors **flexures**
    - **Diffuse xerosis** becomes more prominent
- **Adolescent/adult AD (>12 yo)**
  - **Lichenified plaques** > weeping eczematous lesions
  - Prominent involvement of **flexures**, face, neck (retroauricular) upper arms, back, and acral sites
  - **AD beginning during childhood is a/w more severe, treatment-resistant disease as in adults**
  - May manifest as **isolated prurigo nodularis, hand or eyelid dermatitis**
- **Senile AD**: marked xerosis rather than typical AD lesions
- Pruritus
  - **Worse in evening**
  - **Triggers: wool clothing, sweat, and stress**
- **Associated features of AD**: xerosis, **ichthyosis vulgaris**, **keratosis pilaris**, **palmoplantar hyperlinearity**, **Dennie-Morgan lines**, **periorbital darkening**, **circumoral pallor**, **anterior neck folds**, **Hertoghe sign (diminished lateral eyebrows)**, **white dermatographism**, follicular prominence (favors darker skin types), **"allergic shiners"** (grey infraorbital discoloration), and **exaggerated linear nasal crease ("allergic salute")**
  - Children have ↑ incidence of: **pityriasis alba** (hypopigmentation seen on face/neck; more common in **darker skin types** and more visible after sun exposure), **lichen spinulosus**, nummular dermatitis, dyshidrotic eczema, and **juvenile plantar dermatosis**
- **Infectious complications**: secondary to impaired barrier function and immunologic factors
  - Bacterial: impetiginization w/ *S. aureus* > *S. pyogenes*
  - Viral: **eczema herpeticum**, molluscum dermatitis, and **eczema vaccinatum** (seen w/ smallpox vaccination)
- **Ocular complications**: **atopic keratoconjunctivitis** (adults), **vernal keratoconjunctivitis** (children, warm climates), **posterior subcapsular cataracts**, **keratoconus** (elongation of the cornea), and retinal detachment

### Regional variants

- **Ear**: erythema/scaling/fissuring under earlobe and retroauricular region
- **Eyelid**: lichenification of periorbital skin
- **Nipple dermatitis**
- **Frictional lichenoid eruption**: occurs during spring and summer in boys on **elbows/knees/dorsal hands** (clusters of small 1–2 mm lichenoid papules)
- **Hand**: may be **intrinsic** (atopic, psoriasis, dyshidrotic, hyperkeratotic), **extrinsic** (irritant or water exposure, or allergic), or **infectious** (tinea, *S. aureus*) in nature
  - **Dyshidrotic eczema on lateral fingers and palms: "tapioca-like," firm and deep-seated pruritic vesicles**
    - Pathogenesis is multifactorial (irritant, atopic, and allergic contact)
    - Often chronic and recurrent/relapsing

- **Diaper** (napkin dermatitis; please refer to [Pediatric Dermatology](#) chapter)
- **Id reactions** (autosensitization)
  - Classic example: a vesicular eczematous id reaction of the hands arising in a pt w/ **tinea pedis**; secondary id reaction resolves when underlying dermatosis is treated
- **Juvenile plantar dermatosis** (please refer to [Pediatric Dermatology](#) chapter)
- **Lip** (cheilitis sicca): **irritant contact dermatitis** (including **"lip-licker's eczema"**) > allergic contact dermatitis (**fragrance mix most commonly**) > atopic dermatitis > eczema of unknown cause
  - Worse in winter; **vermillion lip most affected**
- **Head and neck**: occurs post-puberty, *Malassezia* may aggravate

### Histopathology

- Acute: **prominent spongiosis**, intraepidermal vesicles/bullae, and perivascular lymphohistiocytic inflammation w/ eosinophils
- Subacute: **milder spongiosis w/ ↑ acanthosis**; lacks vesicles
- Chronic: **marked irregular to psoriasiform acanthosis** (key feature), minimal to no spongiosis, +/- dermal fibrosis, and hyperkeratosis

### Laboratory testing

- IgE not typically helpful
- In some patients **identification of allergens via fluorescence enzyme immunoassays, RAST testing, skin prick testing, and atopy patch testing** may be warranted
- Consider testing for food hypersensitivity (eggs, milk, peanuts, soy, and wheat) in children with severe/refractory AD and reliable history of immediate reaction, or worsening dermatitis after ingestion of specific food
  - **Food allergy most commonly causes a type I immediate hypersensitivity reaction**
  - 10%–15% of children with severe AD have coexistent food allergies
- Consider testing for aeroallergens (dust mites, pollen, animal dander, and fungi) in teens/adults w/ severe or refractory AD on exposed skin surfaces
  - ↑ incidence of airborne allergy w/ ↑ age

### Treatment

- Review Guidelines in the Care and Management of Atopic Dermatitis published in the JAAD 2013–2014
- Education regarding emollients, short lukewarm baths w/ minimal soap, bleach baths (especially if history of skin infection), and wet dressings +/- topical steroids
- Avoid **irritants**: overheating, wool, sweating, saliva, harsh soaps, fabric softeners, bubble baths, and **smoke**
- Treatment ladder that ranges from topical treatments (steroids, and calcineurin inhibitors) to light therapy (nbUVB > bbUVB, UVA1, and PUVA) to systemic meds



(systemic corticosteroids, cyclosporine, azathioprine, MME, and MTX) depending on severity

- **Topical corticosteroids are mainstay**
- May experience rebound flares after short courses of systemic steroids
- **Sedative antihistamines** as adjunctive treatment for itch
- Treat secondary infections (AD skin has ↓antimicrobial peptides and a compromised barrier → ↑infection risk)
- **Primary prevention via breastfeeding** or formulas w/ hydrolyzed milk products for the first 4 to 6 months of life is protective in high risk AD patients
  - Evidence suggests that prenatal, followed by postnatal **probiotic supplementation**, and postnatal prebiotic supplementation, may ↓risk of AD
    - Prebiotics = non-digestible plant fibers/ oligosaccharides that help nourish the “good gut bacteria”
- If true IgE-mediated allergy → practice avoidance or undergo allergen-specific immunotherapy through allergist

#### Prognosis/clinical course

- AD tends to clear in most children by puberty
  - **Classic teaching: 75% resolve by adolescence** (however, new study suggests that only 50% remit by early adulthood)
- If disease persists beyond childhood → tends to be chronic

### Asteatotic dermatitis (eczema craquelé)

- Typically >60 yo; **worse in winter**
- In elderly, ↓**natural moisturizing factor** → ↓water binding capacity → when humidity is low in wintertime, get skin dehydration/xerosis → scaling, cracking, and dermatitis
- Xerotic skin w/ fine cracking (resembles “**cracked porcelain**” → hence *eczema craquelé*), erythema and scale +/- oozing, and crusting
- Pruritic; favors **lower legs**
- Histology: **xerosis (compact stratum corneum)** + spongiotic dermatitis
- Rx: emollients to treat xerosis/prevent flares (applied immediately after bathing); avoid aggravating factors; topical corticosteroids and TCIs for flares

### Nummular dermatitis

- Unknown pathogenesis
- Associated factors: external irritants, venous HTN, infection, atopy, and xerosis
- **Round or coin-shaped (“nummular”)** pink plaques often on **extremities**; **very pruritic**; can have acute (eczematous) or chronic (lichenified) appearance
  - Secondary *Staph* infection common
- Histology: subacute-chronic spongiotic dermatitis
- Rx: **mid to high potency topical steroids** (ointments preferable to creams), TCIs, and phototherapy; good skin care w/ emollients

### Progesterone dermatitis

- Cyclic flares of dermatitis during **luteal phase** of menstrual cycle (starts **1 week before menses** → resolves a few days after menses)
- Variable morphology (urticarial, vesicles, and oral erosions)
- Diagnostic test = **intra-dermal injection of progesterone** → skin reaction
- Rx = **OCPs** or tamoxifen to inhibit ovulation
- Estrogen dermatitis (chronic w/ exacerbations just prior to menses; Rx = tamoxifen) is major DDx → intra-dermal estrone test distinguishes

### Contact dermatitis

#### Epidemiology

- Irritant (ICD, 80%) > allergic (ACD, 20%)
- Occupations most affected:
  - Manufacturing/mining (UK)
  - Agricultural workers (USA)
- Most common causes of ACD:
  - **Nickel** (worldwide)
  - **Poison ivy** (USA)
- ICD is the most common form of occupational skin disease
  - Petrochemical, rubber, plastic, metal, and automotive industries
  - Causes: soaps > wet work > petroleum products > cutting oils > coolants
- Infants, elderly, and those w/ AD have increased risk, due to ↑penetration of contactants

#### Pathogenesis

- **ICD: direct damage of keratinocytes** by irritant; **not immune-mediated**, does NOT require previous sensitization
  - Acute ICD: strong irritants (acids/bases) → direct cytotoxic damage to keratinocytes
  - Chronic ICD (more common): repetitive use of mild irritants (soap/water) → over time removes lipid and water-retaining substances of keratinocytes → ↑transepidermal water loss, ↑epidermal turnover, inflammation
  - Frictional irritants: repeated rubbing, vibration, and pressure
  - Cold temperature, low humidity → ↑permeability to irritants
  - Occlusion/maceration/↑humidity may → ↑permeability of water-soluble compounds
- **ACD: immune-mediated, delayed-type (type IV) hypersensitivity, initial sensitization** to allergen is required
  - Sensitization can occur with just a few exposures, or after years of exposure
  - Subsequent **reexposure** to allergen → T-cell mediated release of cytokines/chemotactic factors → **eczema within 48 hrs**
    - Only need exposure once every 3 weeks to keep allergic reaction going

- Cross-reactions and co-reactions can occur:
  - Cross-reaction: sensitization to one compound results in sensitization to compounds w/ a **similar chemical structure** (e.g., **poison ivy and mango peel**; neomycin and gentamicin)
  - Co-reaction: sensitization to two chemicals simultaneously because they are **contacted/used together**, but otherwise allergy to one would not result in allergy to the other (e.g., nickel and cobalt; **neomycin and bacitracin**)
- Other allergens: **gold (rings)**, other metals, volatile gases, fragrances/balsam of Peru, neomycin, surfactants, and preservatives

### Clinical features

#### Irritant contact dermatitis

- Clinical presentation variable; **burning** may be more common than itch
- **Hands most common** site of involvement; face is #2
- Ranges from acute ICD with vesiculation/necrosis that has more clearly defined margins to chronic ICD w/ dryness, scaling, lichenification, and fissuring
- Pustular/acneiform irritant ICD: metals, croton oil, mineral oils, tars, greases, cutting and metal working fluids, and naphthalenes
- Airborne ICD: resembles photoallergic reaction, but involves **upper eyelids, philtrum, and submental region**
- Phytophotodermatitis: **fucocoumarins + light (UVA; 320–400nm)** → erythema +/- blistering (24–72 hrs postcontact) followed by **hyperpigmentation** (1 to 2 weeks later)
  - Berloque dermatitis: pigmentation of neck/trunk/arms from **cologne** application containing **bergamot oil** (bergapten = 5-methoxypsoralens; a furocoumarin)
- Can have concomitant ulceration, folliculitis, miliaria, pigmentary alterations, alopecia, and urticaria

#### Allergic contact dermatitis

- Acute: erythema/edema/papules/**oozing/vesiculation**; sharp demarcation between normal and involved skin
- Subacute: ↑**acanthosis**, ↑**crusting/scaling**, and ↓vesiculation
- Chronic: **marked lichenification/fissuring/scaling, no vesicles, less well-defined** than acute, and may spread beyond site of exposure
- Distribution depends on exposure:
  - **Linear** streaks on extremities: **rhus** (poison ivy/poison oak/poison sumac)
  - Fingertips in florists: flowers (**tulips #1**)
  - Scalp is fairly resistant to allergens → often only the surrounding skin is involved (neck, cheeks, and postauricular)
    - Allergens: hair products (especially dyes), perms, and rinse off products (shampoo)
  - Perioral/baboon syndrome: flavorings, foods, cosmetics, shellac, meds, and sunscreens
  - Periocular/eyelid:
    - Nail products (**tosylamide** > acrylates, formaldehyde, resin, glutaraldehyde, and benzalkonium chloride)
    - Cosmetics (false eyelashes, adhesives, mascara, rubber sponges for make-up, and eye-shadow)

- Lips: gallates, dyes, flavorings, sunscreens, and propolis
- Earlobe: **nickel**
- Neck: fragrances and hair products
- Wrist: chromates (leather)
- Hands: gloves (latex, rubber (thiuram), and acrylates in medical gloves)
- Clothing dermatitis: **saves the folds (axillary vault)** and is **accentuated where clothing fits tightly** (waistline); most common allergens:
  - Fabric finishers (i.e., anti-wrinkle and stain repellent): **formaldehyde and formaldehyde releasers**
  - Dyes (**disperse blue dyes 106 and 124**)
  - Rubber (bleached underwear → bleaching causes release of carbamates)
- Cosmetics dermatitis: commonly on face/neck; **fragrances are #1 cause**, preservatives are second most common
- Perianal: lidocaine and preservatives (e.g., **MCI/MI**)
- Shoe dermatitis: **saves toe webs**, begins on base of great toe and spreads over the dorsal surface, plantar surfaces generally spared)
  - Causes: adhesives (**colophony**, p-tert-butylphenol formaldehyde resin), rubber and rubber accelerators (**mercaptobenzothiazole**), leather (**chromates**), and dyes
- Ulcers: **bacitracin, neomycin, and lanolin**
- Oral stomatitis: dental fillings (**mercury/gold/amalgam** → **lichenoid** reaction), epoxy resins, and **flavoring** (mint/cinnamon)
- Airborne ACD: usually from plants (**Compositae = #1 cause**), but other chemicals also implicated
- Systemic ACD: diffuse dermatitis due to systemic allergen (e.g., systemic dermatitis from IV aminophylline in pt w/ ethylenediamine sensitivity)
- Occupational ACD: rubber > nickel > epoxy and other resins > aromatic amines
- Adhesives
  - Most tape reactions are ICD
  - ACD to tape: rubber, resins, and acrylates

#### Histopathology

- ICD: mild spongiosis, **scattered necrotic keratinocytes**, and mild perivascular inflammation
- ACD: **spongiotic dermatitis** (may be acute/subacute/chronic, depending on stage), more prominent dermal inflammation
  - vs ICD: ↑spongiosis, ↑dermal inflammation w/ eosinophils, and lacks necrotic keratinocytes

#### Laboratory testing

- **Patch testing will confirm diagnosis of ACD**
  - Tailor the examined allergens to patient; NEVER apply unknown product during patch testing (can cause severe reaction/burn); determine relevance of any positive reaction



- Patches applied to upper back area free of dermatitis on day 0; patches removed at 48 h (day 2); reactions recorded day 2 (first reading) and day 3–7 (second reading, usually 96 h)
  - Reactions that **fade** between first and second readings = **irritant**
  - Reactions that **continue or develop** between first and second readings = **allergic**
  - **Delayed positive patch tests** (arise after 7 days) can be seen with: **gold**, neomycin, dodecyl gallate, palladium, *p*-phenylenediamine, and **corticosteroids**
  - Gold can cause a persistent positive reaction at the site of patch testing
- TRUE test: currently three panels of 12 allergens each ([www.truetest.com](http://www.truetest.com))
  - Not as complete as comprehensive patch testing
- Repeat open application test (ROAT): use if patient cannot do patch test, or to confirm patch test results
  - Apply product to single clear area of skin twice daily for 1–2 weeks → monitor for reaction
- Material safety data sheets (MSDS) and workplace visit can help determine what workers are handling

### Specific contactants

#### Irritant contact dermatitis

- Fiberglass dermatitis
  - Injury via skin penetration → pruritus/tinging → pink papules
  - Rx: talcum powder
- Bodily fluids (e.g., **saliva, urine, feces**) and water
  - Rx: provide barrier protection (e.g., **zinc oxide** paste, improved hygiene)
- Alkalis
  - Strong alkalis are corrosive: dissolve keratin and penetrate deeply → **worse rxns than acids**
  - Ca/Na/K hydroxides; ammonia; lye
  - Soap, detergent, bleaches, and depilatories
  - Treatment: apply weak acid (vinegar or lemon juice)
- Acids
  - Powerful acids are corrosive and weaker ones are astringent (a compound that shrinks or constricts tissues)
  - Sulfuric acid
    - Causes severe burns, produces brownish staining
    - Brass and iron workers, battery makers, jewelers, weapon of vitriol attacks (“acid throwers”)
  - Nitric acid
    - Distinctive burns with yellow discoloration
    - Explosives, fertilizer
  - Hydrofluoric acid
    - Penetrates very deeply due to low dissociation rate → **severe damage to bones, nerves; exquisitely painful**; symptoms may be delayed for up to 24 hrs
    - Used for dissolving/etching glass in semiconductor industry
    - Rx: neutralize w/ **calcium gluconate** gel, seek emergency care
  - Hydrochloric acid
    - Superficial burn → produces blisters
- Oxalic acid
  - Paresthesia of fingertips; cyanosis; gangrene
- Phenol
  - Used in cosmetic peels
  - Produces **white eschar** and temporary anesthesia; systemic absorption → **glomerulonephritis and arrhythmias**
  - **Neutralized by 65% ethyl or isopropyl alcohol**
- Plants
  - May cause non-immunologic contact urticaria, irritant dermatitis (mechanical or chemical), phytophotodermatitis, and allergic contact dermatitis (discussed in ACD section)
  - **Non-immunologic contact urticaria:**
    - Urticaceae family (nettle family): *Urtica dioica*
      - ◆ Sharp hairs on plants contain toxins (**histamine, serotonin, and acetylcholine**) → rapid edema, pruritus, and burning
  - **Mechanical ICD:**
    - Opuntia spp. (**prickly pear**)
      - ◆ Causes **glochid dermatitis**: mechanical ICD as a result of larger spines or smaller glochids (collections of short barbed hairs) that cause penetrating injuries → inoculation of *C. tetani*, *S. aureus*, *S. shenckii*, and atypical mycobacteria
      - ◆ Remove larger pieces w/ tweezers; use glue and gauze for smaller pieces
  - **Chemical ICD (Boards Favorite!):**
    - Bromelin
      - ◆ Ananas cosmosus (**pineapples**)
    - Calcium oxalate
      - ◆ Family Amaryllidaceae/Lilaceae
        - **Daffodil** (*Narcissus* spp.), hyacinth, and tulip bulbs
        - Most common cause of ICD in florists, “daffodil itch”
      - ◆ Family Araceae
        - **Dumb cane** (*Dieffenbachia*; house plant)
      - ◆ Ananas comosus
        - Pineapple (also contains bromelin)
    - Capsaicin
      - ◆ Family Solanaceae
        - Hot peppers
        - Neutralized with acetic acid (vinegar) or antacids
    - Phorbol esters
      - ◆ Family Euphorbiaceae
        - **Croton plant, spurges**, and poinsettias
        - Also contains diterpenes (**latex**)
        - May cause temporary blindness
    - Protoanemonin/**ranunculin**
      - ◆ Family Ranunculaceae
        - **Buttercups** and marigolds
        - Classic **linear vesicles** like phytophotodermatitis, but NO hyperpigmentation afterwards
    - Thiocyanates
      - ◆ Family Alliacea
        - Garlic
      - ◆ Family Brassicaceae
        - Black mustard, radish



**Figure 3-6.** Phytophotodermatitis; the patient had rinsed her hair with lime juice in Mexico. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- **Phytophotodermatitis (Boards Favorite!):**
  - Caused by **foucoumarins** in plants + **UVA light (320–400nm)** (Fig. 3-6)
  - **Apiaceae/Umbelliferae**
    - ◆ **Hogweed (*Heracleum*)**, cow parsley, and wild chervil: “**trimmer dermatitis**” after weed whacking
    - ◆ **Parsley, parsnips, celery**, and carrots: “**harvester’s dermatitis**” in gardeners
    - ◆ Flowers easily identified as they are clustered on a stalk and arise from a single point (mnemonic: “**Apiaceae/Umbelliferae** phytophotodermatitis = **Ape** holding an **Umbrella**-looking plant to stay protected from sun”)
  - **Rutaceae**
    - ◆ **Citrus** (lemon, lime, grapefruit), rue
    - ◆ *Citrus bergamia* (bergamot orange): causes **berloque dermatitis**
    - ◆ *Pelea anisate* (**Hawaiian leis**)
    - ◆ Common cause in **bartenders** and spring breakers
    - ◆ “**Mexican beer dermatitis:**” phytophotodermatitis variant that may be widespread rather than linear, due to aerosolization of lime-beer mixture
  - **Moraceae**
    - ◆ Fig and fig leaves
    - ◆ Mulberry
  - **Fabaceae (legumes):**
    - ◆ **Bavachee/scurf pea** (used as vitiligo treatment)
    - ◆ **Balsam of Peru** (*Myroxylon balsamum*, *Myroxylon pereiace*)

### Allergic contact dermatitis

- Specific allergens involved in ACD (refer to Table 3-1)
- ACD due to plants (Table 3-2)
  - **Rhus dermatitis:** **Anacardiaceae** family, *Toxicodendron* species
    - Allergen: **urushiol** (an oleoresin)
      - ◆ Sensitizing ingredient: **pentadecylcatechol**
    - Poison ivy/poison oak/poison sumac
      - ◆ Contained in leaves, stems, and roots
    - Direct contact (plant/fingers) → linear/streaky erythematous vesicles/bullae
    - Indirect contact (pet/burning plant) → diffuse
    - **Black lacquer/spot dermatitis:** sap from *Toxicodendron* species turns black w/ oxidation in stratum corneum
  - **Asteraceae (Compositae):** causes **airborne ACD**
    - Unlike photosensitive dermatitis, involves **eyelids/melolabial folds/submental/retroauricular sulci/antecubital fossae**
    - Classically affects middle-aged men
    - Worse in summer, resolves in winter
  - **Essential oils:** cinnamon oil (cassia), eucalyptus oil, and citrus peel
  - **Exotic hardwoods** (cocobolo/rosewood): can cause erythema multiforme-like reaction
  - **Foods:** variety of vegetables, fruits, and spices can cause ACD
  - **Photoallergic contact dermatitis**
    - Allergen + light (usually **UVA**) → dermatitis via immune mechanisms

### Treatment

- Gold standard is education and avoidance of allergen/irritant
- Additional treatments similar to other dermatitides
- For ICD, many cases resolve spontaneously due to “hardening” phenomenon
- After acute ACD exposure (i.e., poison ivy), whole area/body should be first washed with water – then soap can be considered; systemic corticosteroids over **3 weeks** are very effective

### Stasis dermatitis

- Incompetent valves of lower extremities → venous HTN → capillary distention and leak → extravasation of fluid, plasma proteins, and erythrocytes → edema, hemosiderin deposition, fibrosis, ulceration, inflammation, and microangiopathy
- **Contact sensitization** (often from topical products or medications), irritant factors, and superinfection may complicate the picture
- **Pitting edema and hemosiderin deposits** over distal third of leg, scaling, inflammation, and pruritus or tenderness; skin changes **often begin on medial ankle**; can become lichenified from rubbing
- a/w **lipodermatosclerosis** (stasis panniculitis; “**inverted wine bottle**” appearance w/ tight circular cuff over distal calf from chronic inflammation → adherent skin/subcutaneous tissue/fascia)

**Table 3-1.** High-Yield Allergic Contact Dermatitis Allergens

**Metals and Metal Salts**

*(Pure metals generally do not cause sensitivity; metals in salts more often cause reactions)*

Nickel	<p><b>Most common positive patch test</b> (relevance ≈50%)</p> <p>Sources: jewelry (white gold, 14-carat gold), buckles, belts, cell phones, buttons, zippers, clothing hooks, musical instruments, keys, doorknobs, European coins, and cement</p> <p>Direct relationship between nickel allergy and number of pierced sites</p> <p>Nickel in foods: cocoa, licorice, margarine, peanuts, brown lentils, walnuts, almonds, hazelnuts, and beans</p> <p>Nickel testing: <b>dimethylglyoxime</b> in 10% ammonia test (turns pink in presence of nickel)</p> <p>Safe metals for pts w/ nickel allergy: titanium, platinum, and sterling silver</p>
Chromates	<p>Sources: dyes (<b>green felt fabric on pool table</b>), yellow-green pigment (tattoos/cosmetics), <b>leather (shoe dermatitis)</b>, <b>cement</b>, matches, and crude oils (engine/aircraft workers and photographers)</p> <p>Cross-reacts w/ nickel and cobalt</p>
Cobalt	<p>Sources: metal products, cosmetics, dyes (<b>blue-green dyes</b>, paint, tattoos), <b>glass/pottery, cement</b>, vitamin B12 injections (can lead to intractable hand dermatitis), and artificial joints</p> <p><b>Poral reaction:</b> irritant reaction w/ purpuric pores</p> <p>Cross-reacts w/ nickel and chromate</p>
Mercury	<p>Common cause of <b>oral lichenoid reaction</b> (mercury amalgams)</p> <p>Sources: <b>amalgams</b> (dentistry), insecticides, industry (glues and starch pastes), felt hat workers, etching/artwork, and furs</p>
Gold	<p>Common cause of <b>oral lichenoid reactions</b> and <b>eyelid dermatitis</b></p> <p>Sources: jewelry (hand/facial/eyelid dermatitis) and amalgams/fillings</p> <p>Most frequent cause of <b>persistently positive patch test reactions</b></p> <p>Cross-reacts w/ nickel and cobalt</p>

**Rubber and Rubber Additives**

*Sources: shoes, gloves, adhesives, elastic (if bleached), pacifiers, cosmetic applicators, latex (gloves, balloons, condoms), swim goggles, tires, fungicides (thiurams), and neoprene (synthetic rubber)*

Latex	<p>Derived from Hevae brasiliensis sap</p> <p>Far more likely to cause <b>immunologic contact urticaria</b> (type I hypersensitivity reaction) than type IV delayed-type hypersensitivity reaction</p> <p>Risk factors: <b>healthcare profession, spina bifida</b></p> <p>Latex <b>cross-reacts w/ "Back Passion"</b> (Bananas, Avocado, Chestnut, Kiwi, Passion fruit)</p>
Thiuram (tetramethylthiuram disulfide)	<p>Most common <b>glove allergy</b> and most common allergen in health workers</p> <p><b>Cross reacts with disulfiram</b></p>
Carba mix/carbamates	Released from <b>bleached elastic</b> ; perform use-test (patch test often false negative)
Mercaptobenzothiazole (MBT)	#1 cause of <b>allergic shoe dermatitis</b>
Black Rubber mix	<p>Found in heavy-duty rubber products (tires, rubber balls)</p> <p>May cause purpuric reaction</p>
Dialkyl thioureas (neoprene)	<b>Wetsuit dermatitis</b> and allergy to goggles
p-phenalenediamine (PPD)	<p>Sources: hair dye, black henna (temporary tattoos), <b>black rubber</b> (rubber vulcanization, antioxidant), photograph development, photocopies, printer ink, other darkly colored cosmetics</p> <p><b>Rubber workers</b> p/w eczema of <b>hands</b>, wrists, forearms, eyelids, nose</p>

**Adhesives**

*Substances used for gluing things together*

Rosin (colophony and abietic acid)	Uses: de-epilation waxes, adhesives, painting, chewing gum, <b>violin</b> and other musical instruments
p-tert-butylphenol formaldehyde resin (PTBP)	<p>Used for <b>gluing together leather products</b> (watchbands, leather handbags, shoes)</p> <p>Can cause depigmentation</p>
Epoxy resin (bisphenol A)	<p>Encountered in: <b>PVC and plastic materials</b>, electrical insulation, paint, artists, sculptors, glues</p> <p>Only produce ACD when in their liquid (non-cured, monomeric) state → fully polymerized product is non-sensitizing</p>
Cyanoacrylates	<p>Used for different purposes, depending on specific type</p> <p><b>Ethyl cyanoacrylate:</b> KrazyGlue; used to glue-on <b>artificial nails</b>; is more toxic to skin than butyl- and octyl cyanoacrylates → not used for skin</p> <p>Butyl cyanoacrylate (GluStitch): sutureless skin closures</p> <p>Octyl cyanoacrylate (Dermabond): sutureless skin closures</p>
Methacrylate	<p>Very hard, rigid <b>plastic</b>; may also be used as adhesive in orthopedic and dental prostheses</p> <p>Uses: artificial nail <b>plates</b>, hard contact lenses, adhesive ("bone cement") for <b>artificial joints, dental prostheses</b>, dental sealant</p> <p><b>Diffuses through rubber and polyvinyl gloves → paresthesias</b></p>

**Preservatives**

*Added to anything with water in order to prevent spoilage; most commonly found in personal care products and cosmetics*

Formaldehyde	<p>Frequent sensitizer, but decreased cosmetic use recently (formaldehyde releasers now more commonly used)</p> <p>Found everywhere – meds, textiles/clothing, paints, embalming process, and paper – but most notably <b>wrinkle-free clothing</b></p> <p>100% cotton or cotton/synthetic fiber blends have most formaldehyde</p> <p><b>Polyester has least formaldehyde of any textile</b></p>
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**Table 3-1.** High-Yield Allergic Contact Dermatitis Allergens—cont'd

Formaldehyde-releasing preservatives (chemical compounds that slowly release formaldehyde)	Formaldehyde-releasing preservatives are #2 cause overall of cosmetic-related ACD (fragrances are #1) <b>Quaternium-15 (Dowicil 200)</b> : found in soaps, shampoos, moisturizers; <b>#1 preservative sensitizer</b> in USA <b>Imidazolidinyl urea</b> Diazolidinyl urea DMDM hydantoin
Kathon CG (methychloroisothiazolinone/methylisothiazolinone (MCI/MI))	Found in <b>wet wipes</b> → common cause of perianal ACD Also present in Eucerin and other personal care products
Parabens	Preservative in topical medications, antiperspirants Cross-reacts with <b>PPPASTA family</b> (Para-aminosalicylic acid, <b>PABA</b> , <b>PPD</b> , <b>Azo</b> dyes, <b>Sulfonamides</b> , <b>Thiazides</b> , ester <b>Anesthetics</b> )
Thimerosal (ethyl mercury)	Mercury-containing preservative in <b>vaccines</b> , <b>eye-drop solutions</b> , cosmetics, and nasal sprays <b>Positive thimerosal patch test almost never relevant!</b> → ok to give vaccines even w/ positive patch test <b>Cross-reacts with piroxicam and mercury</b>
Other preservatives	2-bromo-nitropropane-1,3-diol (Bronopol) Euxyl K 400 (methylidibromoglutaronitrile) Benzylkonium chloride Triclosan Benzyl alcohol Tea tree oil
<b>Vehicles, Emollients, and Emulsifiers</b>	
Propylene glycol	Vehicle base in many creams and lotions Also in <b>ECG and lubricant</b> jelly, <b>antifreeze</b> , <b>brake fluid</b> , food dyes/flavorings
Cocoamidopropyl betaine	Non-ionic <b>surfactant</b> found in <b>shampoo</b> , soaps Derived from coconut oil
Ethylenediamine	Found in topical steroid and antifungal creams ( <b>Mycolog</b> ) Cross reacts w/ <b>aminophylline</b> and hydroxyzine → can develop systemic ACD if allergic and receive aminophylline!
Lanolin	Used in emollients Allergen is <b>wax-wool alcohol</b> (derived from sheep) Allergy common among <b>leg ulcer</b> pts Cross-reacts w/ <b>Aquaphor</b> and Eucerin
Propolis	Made by <b>bees</b> from resinous exudates of plants Most notable for <b>ACD of lips</b> (lip balms)
<b>Fragrances</b>	
<b>Fragrance allergy is #1 cause of all cosmetic-related ACD</b> ; almost all cosmetics contain fragrance; "fragrance free" ≠ no fragrance (still may have masking fragrances!); fragrances are used for <b>cologne</b> , <b>perfumes</b> , and <b>food flavoring</b> ; <b>patch test to balsam of Peru and fragrance mix detects 90% of fragrance allergies</b>	
Fragrance mix	Patch test to mixtures of eight fragrances (cinnamic alcohol, cinnamic aldehyde, amyl cinnamic alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, oak moss absolute) Rash typically limited to face, hands, arms, and tongue Cross-reaction w/ propolis, colophony, turpentine
Balsam of Peru	Derived from <b>Myroxylon pereirea</b> tree Detects 50% of fragrance-related ACD
<b>Hair Products</b>	
p-phenylenediamine (PPD)	Potent sensitizer! Sources: <b>hair dye</b> , <b>black henna (temporary tattoos)</b> , <b>black rubber</b> (rubber vulcanization, antioxidant), <b>photograph</b> development, photocopies, printer ink, and other darkly colored cosmetics <b>Hairdressers</b> , photographers, rubber workers: eczema of <b>hands</b> , wrists, forearms, eyelids, nose Clients who get hair dyed: <b>scalp and hairline dermatitis</b> <b>Beard dermatitis</b> in those who dye their beards Note: <b>natural henna</b> ( <i>Lawsonia inermis</i> ) is a traditional red-brown dye used in South Asian cultures; <b>does not commonly cause ACD</b>
Perms	Alkaline (home) perm: <b>ammonium thioglycolate</b> (rare sensitizer, more likely to cause ICD than ACD) Acid (professional/salon) perm: <b>glyceryl monothioglycolate</b> (allergen); a common sensitizer, remains in hair shaft for >3 months; penetrates rubber and vinyl gloves Neutral perm: cysteamine hydroxychloride (uncommon sensitizer)
Hair bleach (contains ammonium persulfate and peroxides)	<b>Ammonium persulfate</b> → <b>contact urticaria</b> reaction and generalized histamine reaction
<b>Nail Products</b>	
Tosylamide (toluene-sulfonamide) formaldehyde resin	<b>Nail lacquer/polish</b> Very common cause of <b>eyelid</b> , neck, and <b>finger/periungual dermatitis</b>
Artificial nails	Ethyl cyanoacrylate: KrazyGlue; used to <b>glue-on</b> artificial nails <b>Methacrylate</b> : rigid plastic material, forms artificial (acrylic) <b>nail plates</b>
<b>Medications</b>	
Transdermal patches	Clonidine has highest rate of sensitization

Continued

**Table 3-1.** High-Yield Allergic Contact Dermatitis Allergens—cont'd

Antihistamines	Doxepin > diphenhydramine
Anesthetics ( <b>esters</b> >> amides)	<p>Esters = <b>one "i" = benzocaine</b> (#1 sensitizer; used for <b>hemorrhoids</b>, toothaches, and sore throats), procaine, tetracaine</p> <p><b>Esters cross react w/ "PPPASTA" family</b> (PPD, PABA, Para-aminosalicylic acid, Azo dyes, Sulfonamides, Thiazides, ester Anesthetics)</p> <p>Amides = two <b>"i's"</b> = dibucaine, lidocaine, mepivaine, and prilocaine</p> <p>Cross reactivity: occurs for drugs within each class, but rarely between classes</p>
Antibiotics (Neomycin, Bacitracin, Polymyxin)	<p>Late reactions on patch testing (day 7)</p> <p>Risk factors: use on <b>chronic leg ulcers</b>, chronic otitis externa, post-operative application</p> <p>Co-reactions may occur with all, but most common with <b>neomycin</b> and <b>bacitracin</b></p> <p>Cross-reactions: <b>neomycin and aminoglycosides</b> (gentamicin, tobramycin)</p>
Corticosteroids	<p>Grouped into categories based on allergenic potential. Each group with standardized screening allergen for patch testing:</p> <ul style="list-style-type: none"> <li>• <b>Group A</b> (screening agent = <b>Tixocortol pivalate</b>): <b>most frequently allergenic</b>; includes hydrocortisone, prednisone, prednisolone, and methylprednisolone</li> <li>• <b>Class B</b> (screening agent = <b>Budesonide</b>): includes triamcinolone, desonide, fluocinolone, fluocinonide, halocinonide, and hydrocortisone butyrate</li> <li>• <b>Class C</b> (screening agent = <b>Betamethasone</b>): <b>least allergenic</b>; includes betamethasone, desoximetasone, dexamethasone, and flucortisone</li> <li>• <b>Class D</b> (screening agent = <b>Hydrocortisone-17-butyrate</b>): includes mometasone, acloemethasone, betamethasone valerate, and clobetasol <ul style="list-style-type: none"> <li>■ Class B and D cross-react with each other</li> <li>■ On patch testing, positive test may be an allergenic ring at edge of patch test site (steroid suppresses allergic response in center)</li> <li>■ <b>Delayed reading important!</b></li> </ul> </li> </ul>
Nitrogen mustard/methlorethamine	ACD occurs in <b>66% w/ aqueous</b> solution, but <b>&lt;5% w/ ointment</b>
Sunscreens	<p><b>Oxybenzone</b> (UVA): <b>most common</b> sunscreen allergen</p> <p>PABA/padimate O (UVB): no longer commonly used; <b>PABA cross reacts w/ other "PPPASTA" allergens</b> (PPD, PABA, Para-aminosalicylic acid, Azo dyes, Sulfonamides, Thiazides, ester Anesthetics)</p> <p>Zinc oxide and titanium dioxide (physical sun blockers): do NOT cause ACD</p>
<b>Miscellaneous Allergens</b>	
Disperse blue dyes	Disperse blue dyes <b>106 and 124</b> are best screening agents Spares axillary vault
Dimethylfumarate	Antifungal agent used to prevent mold growth in <b>leather couches ("Chinese sofa dermatitis") and shoes</b>

**Table 3-2.** ACD Due to Plants

Family	Sensitizer	Sources	Cross Reaction
Anacardiaceae (Toxicodendron genus)	Pentadecylcatechol in oleoresin (urushiol)	Poison ivy/poison oak/poison sumac	<b>Japanese lacquer tree; cashew</b> nut (nutshell); <b>mango</b> rind/leaves/sap; Indian marking nut; <b>ginkgo</b> (fruit pulp); Brazilian pepper tree
Alstromeriaceae	Tulposide or tulipalin A	Peruvian lily (Alstromeria) favors dominant hand	
Liliceae	Tulipalin A/B	Tulip bulb (favors dominant hand, usually first/second fingertips), asparagus, hyacinth	
Parmelia	d-usnic acid	Lichens	
Pinaceae	Colophony (abietic acid)	<i>Pinus palustris</i> (pine) tree	Balsam of Peru, turpentine, colophony, benzoin, wood tars, spices
Asteraceae (Compositae)	Sesquiterpene lactone	Ragweed, <b>dandelion</b> , pyrethrum, mugwort, <b>chrysanthemum</b> (dominant hand), weeds, feverfew, artichoke, daisy, <b>sunflower</b> , endive, arnica, marigold, chamomile	Permethrin
Alliaceae	Diallyl disulfide	Onions, garlic ( <b>non-dominant hand w/ hyperkeratosis/fissuring of thumb, index, and middle finger tips</b> ), chive	
Primulaceae	Primin	Primrose (dominant hand)	
Myrtaceae	D-limonene	Tea tree oil/maleuca oil	



- Atrophie blanche and ulceration from venous changes can occur (**typically medial supramalleolar region**)
- Histology: spongiotic dermatitis, **lobular capillary hyperplasia** +/- fibrin cuffing, **hemosiderin**, and **fibrosis** of dermis and SQ fat septae (later stages)
- Rx: manage venous HTN w/ **compression stockings** and elevation
- For dermatitic component: emollients/topical steroids

### Autosensitization (id reaction and disseminated eczema)

- Secondary eczematous lesions develop in sites distant from primary exposure site (usually allergic contact dermatitis +/- stasis dermatitis (>60% w/ **contact dermatitis** and stasis dermatitis develop id reactions); can also occur in **tinea pedis**)
- Disseminated lesions appear days to weeks after primary lesion
- Eczema tends to be **ill-defined and symmetric**, often occurring in analogous anatomical sites (e.g., palms, soles, extremities)
- Pathogenesis unknown but possibly related to:
  - Hematogenous dissemination of allergens
  - Desensitization threshold in distant skin sites after primary inflammation
  - Circulating activated memory T-cells
- Rx: topical steroids, systemic antihistamines, treatment of any underlying causes

### Contact urticaria (CU)

#### Epidemiology

- In Finland, cow dander > natural rubber latex > flour/grain/feed
- Bakers > agricultural workers > butchers
- Risk factors: **atopy**, hand dermatitis, and allergy to fruits (kiwi, avocado, banana, and melon)

#### Pathogenesis

- **Immunologic CU**: mediated by allergen-specific IgE on mast cells → mediator release (e.g., histamine); since IgE mediated can be a/w **anaphylaxis**
  - **Raw vegetables/meats**: **potato** (#1 and often a/w asthmatic response), celery (more likely to cause anaphylaxis), raw meat, fish, and shellfish
  - **Latex**:
    - Most common in **healthcare workers** (up to 10% incidence)
    - Increased risk in **spina bifida patients** and atopics
    - Type I reaction to latex is much more common than type IV (delayed type hypersensitivity)
    - Symptoms include itching and swelling of hands within minutes of applying gloves → resolves within 1 h; chronic exposure may lead to chronic hand eczema
    - **Aerosolized glove powder** or mucosal exposure may induce **anaphylaxis**
    - 50% have **cross-reaction** w/ "**back passion**" (bananas, avocado, chestnuts, kiwi, passion fruit)

- Other causes: henna, **ammonium persulfate** (hair bleach), and **bacitracin** (may lead to anaphylactic reactions when applied to chronic leg ulcers)
- **Non-immunologic CU**: more frequent, occurs in any exposed individual, and **much lower risk of anaphylaxis**
  - **Urticaceae/stinging nettles** (#1), euphorbiaceae (spurge nettle), caterpillars, and jellyfish
    - Agents lead to direct release of histamine, acetylcholine and serotonin
  - Other causes: **DMSO**, sorbic acid, benzoic acid, and cinnamic aldehyde
- **Protein contact dermatitis**: dermatitic reaction to protein-containing products in foods/animal products; reactions both allergic (type I and/or type IV) and non-allergic

#### Clinical features

- Pruritic cutaneous urticaria (wheal and flare) within 1 hr of exposure (3–5 min for stinging nettles); resolves in 24 hrs
  - Oral allergy syndrome = mucosal CU (type of immunologic CU)
- Foods are common cause of CU; can get cross-reactions between foods and other topical/aeroallergens:
  - Birch pollen allergy a/w CU to various fruits/vegetables (apples, pears, and cherries)
  - **Latex CU a/w cross allergy to "back passion"** (bananas, avocado, chestnuts, kiwi, passion fruit)

#### Laboratory testing

- Standard closed patch testing method is ineffective → use **open patch test** instead
  - Open patch test: apply substance to forearm and wait 30 min for wheal and flare response; if no response can wait 30 min longer
  - Open patch testing is superior to prick, scratch, and intradermal testing as these can lead to anaphylaxis
- RAST testing detects 75% of latex allergies

#### Treatment

- Varies depending on severity: avoidance and **antihistamines (most cases)**, systemic steroids (generalized urticaria or asthmatic reactions), and epinephrine + supportive care (anaphylaxis)

## 3.3 INTERFACE DERMATITIS

### Vacuolar interface dermatitis

### Autoimmune connective tissue disease (AICTD)

Discussed in [Section 3.5](#)

### Erythema multiforme (EM)

#### Epidemiology

- Predominantly young adults (M ≈ F) in spring and fall

### Pathogenesis

- 90% of cases are caused by infection:
  - HSV (HSV1 > HSV2) infection by far **most common trigger**
    - Herpes-associated EM (HAEM) is most common cause of **EM minor (von Hebra's disease)**
    - Herpes labialis outbreak most commonly precedes EM by 1–3 weeks
  - *Mycoplasma pneumoniae*: severe **mucous membrane** involvement (simulates SJS) and atypical papular target lesions; most common cause of EM **major**
- Less common causes:
  - *Histoplasma capsulatum*: commonly have **concomitant erythema nodosum**
  - Drug-induced (<10%): NSAIDs, antibiotics, sulfonamides, antiepileptics, and TNF- $\alpha$  inhibitors
  - Other: radiation-induced, idiopathic, and chronic oral EM

### Clinical features

- Abrupt onset of numerous symmetric, fixed red macules → papules → “target” lesions (mixture of typical targets and papular atypical targets)
- **Typical target (classic primary lesion of EM)**:
  - **Three zones**: dusky, vesicular or necrotic center; elevated, edematous pale surrounding ring; outer rim of macular erythema
  - Well-demarcated
  - Favors **face and distal extremities** (UE > LE; dorsal hands and forearms most common) (Fig. 3-7)
- **Papular (elevated) atypical target**:
  - Only two zones, but is **palpable**
  - Ill-defined peripheral border
    - Important clinical pearl: **macular** (non-palpable, non-elevated) atypical targets are seen in SJS/TEN, but not EM!
- Presence of elevated/papular target lesions and acrofacial distribution allow for reliable distinction from SJS/TEN
- EM **minor**: target lesions w/ minimal mucosal involvement and no systemic symptoms



**Figure 3-7.** Erythema multiforme involving the dorsal hands and penis. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- EM **major**: target lesions w/ severe mucosal involvement and **systemic symptoms** (fever, arthralgias)
  - Buccal mucosa and lips most common mucosal sites (> ocular, genital)
  - Primary mucosal lesions are raised targets → rapidly become painful erosions
- Oral EM (clinical variant): middle-aged women w/ recurrent disease limited primarily to oral cavity

### Histopathology

- Individual keratinocyte apoptosis, **prominent basal vacuolar change**, spongiosis w/ lymphocyte exocytosis, moderately dense superficial dermal perivascular lymphohistiocytic infiltrate (Fig. 3-8), and **absent/rare eosinophils** (vs SJS/TEN)
  - vs SJS/TEN: ↑↑dermal inflammation, ↓epidermal necrosis, and ↓eosinophils

### Laboratory testing

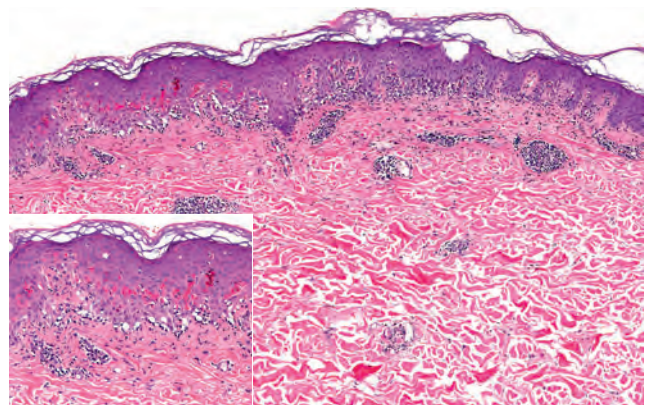
- 80% have detectable HSV DNA by PCR in early erythematous papules or outer rim of targets

### Treatment

- Most cases: symptomatic treatment
- Severe cases: consider systemic steroids or immunosuppressants
- **HSV prophylaxis to prevent future outbreaks**
  - Antiviral prophylaxis (Valtrex 1 gm/day or Famvir 250 mg/day): ↓frequency and duration of recurrence in 90% of HAEM cases

### Prognosis/clinical course

- Acute onset of lesions over 24 hrs → eruption fully developed by 72 hrs → self-resolves without sequelae within 2 weeks
  - **Exceptions**: EM major w/ **severe mucosal involvement** → persists for up to 6 weeks and may be a/w ocular complications (if proper eye care not instituted)



**Figure 3-8.** Histopathologic features of erythema multiforme. Early lesion – focal sites of apoptosis of keratinocytes with an interface dermatitis and vacuolar degeneration of the basal layer (insert). A perivascular lymphocytic infiltrate is also present. Courtesy, Lorenzo Cerroni, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

## Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN, Lyell's syndrome)

### Epidemiology

- Overall incidence of SJS/TEN = five cases/million people annually
- F > M; **elderly more frequently affected**
- Groups with ↑risk of SJS/TEN:
  - Slow acetylators genotypes
  - HLA-B\*1502 (Asians and East Indians exposed to carbamazepine; up to 220-fold ↑risk)
  - HLA-B\*3101 (Europeans exposed to carbamazepine)
  - HLA-B\*5701 (abacavir)
  - HLA-B\*5801 (Han Chinese exposed to allopurinol)
  - HLA-DQB1\*0601 (white patients with SJS + ocular complications)
  - AIDS patients (1000-fold ↑risk)
  - Patients undergoing radiotherapy + anticonvulsant therapy

### Pathogenesis

- Exact mechanism still being elucidated, but the key players are known:
  - Drug
    - Binds to MHC I complex or other intracellular peptides → forms antigen recognized by cytotoxic CD8+ T-cells → downstream proapoptotic effects
  - Granulysin
    - Currently felt to be the **major mediator of apoptosis** in SJS/TEN
    - Found in cytotoxic granules of CD8+ T-cells, NK/T-cells, and NK-cells
    - Secreted granulysin directly damages target keratinocytes → apoptosis
  - FasL (CD95L)
    - Transmembrane protein of TNF family, found on cytotoxic T-cells, NK-cells, and keratinocytes
    - FasL binds to the Fas death receptor (CD95/Apo-1) on target keratinocytes → FasL-Fas complex leads to activation of **caspases** → **apoptosis**
  - Granzyme B and perforin
    - Activated cytotoxic CD8+ T-cells exocytose granzyme B and perforin → molecules poke holes in target cell and activate caspases → apoptosis
- SJS/TEN is **almost always drug-induced**
  - Typically occurs 1 to 2 weeks after initiation of med
  - Occurs later with anticonvulsants (within first 2 months)
  - Even within the same class, drugs with longer half-lives are more likely to cause drug reactions and fatal outcomes than drugs with short half-lives
  - Most common culprit drugs:
    - Allopurinol
    - Anticonvulsants
      - ◆ Lamotrigine, carbamazepine, phenytoin, and phenobarbital
      - ◆ Risk highest in first 2 months
      - ◆ Valproic acid does NOT cross-react w/ others
      - ◆ Lamotrigine does not cross-react w/ aromatic anticonvulsants

- Antibiotics (**sulfonamides** > β-lactams, cephalosporins, minocycline, quinolones, and antifungals)
- NSAIDs
- NNRTIs (**nevirapine, abacavir, efavirenz, and etravirine**)
- Other notable causes:
  - ◆ *Mycoplasma pneumoniae* (more commonly causes EM major), contrast medium, dengue virus, and cytomegalovirus

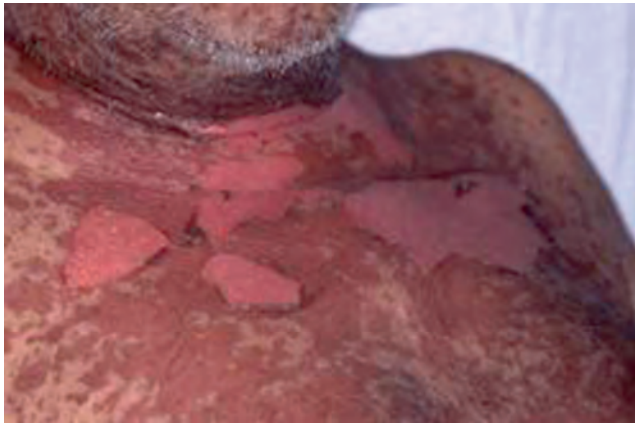
### Clinical features

- SJS and TEN are two intimately related, potentially life-threatening adverse drug reactions that **differ only in their degrees of severity**, as determined by degree of epidermal detachment (% BSA):
  - SJS: <10%
  - SJS-TEN overlap: 10%–30%
  - TEN: >30%
- Skin findings preceded by **prodrome** (fever, malaise, anorexia, and rhinorrhea) → **atypical targetoid macules**, mucocutaneous erythema, and skin pain →  **dusky plaques** w/ full-thickness sloughing
- **Mucosal involvement** almost always present (92%–100% of SJS; ~100% of TEN)
  - Erosions and erythema of oral/ocular/genital mucosae
  - Photophobia and painful urination
  - **Eye and genital care is essential** for preventing adverse sequelae
  - Respiratory involvement in 25%
- Characteristic cutaneous lesional morphology:
  - Poorly demarcated erythematous to **dusky macules** of variable size and shape
    - Macules commonly become confluent (TEN > SJS-TEN overlap > SJS)
  - **Flat/macular atypical targets** (macules w/ central dusky hue)
    - Resemble target lesions of EM, but lack three concentric rings and are **flat** (non-palpable)
    - SJS/TEN lacks **raised targets** (vs. EM)!
- **Lesions appear first on trunk** → spreads to neck/face, proximal upper extremities
  - Unlike EM, distal extremities are largely spared
  - Early lesions are erythematous, dusky or purpuric macules, or flat atypical targets of varying size and shape → macules rapidly coalesce → hours to days later full thickness necrosis ensues → dusky red macules develop a grey hue → flaccid blisters develop with positive **Nikolsky** and **Asboe-Hansen** signs (**Fig. 3-9**)
    - (+) Nikolsky sign: **tangential pressure** induces dermal-epidermal cleavage
    - (+) Asboe-Hansen sign: **vertical pressure** (applied to top of a bulla) results in extension of blister onto adjacent previously unblistered skin

### Histopathology

- Early: individual apoptotic keratinocytes scattered about all layers of epidermis; scant dermal lymphohistiocytic infiltrate w/ **eosinophils**





**Figure 3-9.** Toxic epidermal necrolysis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the trunk. (From Schwartz RA1, McDonough PH, Lee BW. J Amer Acad Dermatol. e1–e13; quiz 185–6. doi: 10.1016/j.jaad.2013.05.003. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. Elsevier. 2013)

**Table 3-3.** SCORTEN Criteria

Finding	0 Points	1 Point
Age (yrs)	<40	>40
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	>120
Serum BUN (mg/dL)	<27	>27
Detached or compromised body surface (%)	<10	>10
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<250	>250

**Table 3-4.** SCORTEN-predicted mortality rates

# of Points	Mortality Rate (%)
0–1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

- Later: **confluent full-thickness epidermal necrosis**, subepidermal blister (due to diffuse keratinocyte necrosis); scant dermal lymphohistiocytic infiltrate w/ **eosinophils**

#### Laboratory testing

- **SCORTEN system** relies on seven parameters (Tables 3-3 and 3-4):
  - **Serum bicarbonate (<20 mmol/L) is the single most important risk factor for mortality**
  - **Mnemonic: TAMEBUG** (tachycardia, age, malignancy, epidermal loss >10%, bicarbonate, urea, glucose)

#### Treatment

- Prevention is ideal
  - **FDA recommends routine screening for HLA-B\*1502 in East Asian patients prior to giving carbamazepine, and screening for HLA-B\*5701 in all potential abacavir patients prior to treatment**

- Early Dx is critical!
  - **Prognosis correlated w/ rapidity of drug discontinuation**
  - Drug timeline: typically **meds started 7–21 days prior** (as early as 2 days with reexposure)
- Initiate intensive supportive skin regimen (ICU setting if extensive epidermal detachment) +/- high-dose IVIG, nutritional/fluid/electrolyte support
  - Majority of studies suggest early administration of **high-dose IVIG (2–4 gm/kg over 3–4 days)** → ↓mortality
  - Drug list should be aggressively minimized; especially **avoid drugs w/ long half-lives**
  - Use of systemic steroids and other immunosuppressive drugs is controversial

#### Prognosis/clinical course

- **Ocular sequelae** are most common complication (up to 80%)
  - Dry eye syndrome (most common), entropion, symblepharon, blindness, scarring, and persistent erosions
- Other sequelae: phimosis, vaginal synechiae, nail dystrophy/loss, hair loss, and eruptive nevi
- Mortality:
  - SJS: <5%
  - **TEN: 30%** (reported range: 25%–50%)
    - SCORTEN must be performed during hospital days 1 (within first 24 h) and 3 to maximize predictive value
    - Rapid withdrawal of causative agent ↓risk of death by 30% per day
    - **Death is most commonly due to infection** (*S. aureus* and *Pseudomonas*)
      - ◆ Other causes: transepidermal fluid loss, electrolyte imbalance, inhibition of insulin secretion, and insulin resistance
      - ◆ Wood lamp can be used to identify *Pseudomonas* fluorescence

#### Additional boards factoids

- In 2013 the FDA issued a warning about **clobazam** (benzodiazepine class), an anti-seizure medicine that has been shown to cause SJS/TEN
  - Typically occurs in first 8 weeks, or when drug is stopped and restarted
- Markedly ↑risk of SJS/TEN in **HIV patients** recently shown to be due to loss of skin-protective CD4+/CD25+/regulatory T-cells
- **Sulfonamide antibiotics do NOT cross-react w/ non-antibiotic sulfonamides** (HCTZ and hypoglycemic agents)
- Serologic tests for granulysin (80% sensitivity and 95% specificity) and high mobility group protein B1 (HMGB1) have been shown to differentiate SJS/TEN from ordinary morbilliform drug eruptions

#### Pityriasis lichenoides

- PLEVA (acute) and PLC (chronic) represent two ends of a disease spectrum; both are characterized by **recurrent crops of self-resolving lesions**

- Etiology unclear; may represent response to infections/drugs, or may represent a low-grade T-cell lymphoproliferative disorder
- Pityriasis lichenoides et varioliformis acuta (PLEVA) (Fig. 3-10)
  - Rapid onset of widespread (**trunk, buttock, and proximal extremities** > other sites) pink papules → evolves into vesicular, ulceronecrotic, purpuric, and crusted papules → **heals w/ varioliform scars**
    - **Febrile ulceronecrotic Mucha-Haberman disease** (PLEVA variant): severe form w/ high fever, constitutional symptoms, lymphadenopathy, arthritis, mucosal, pulmonary, and GI involvement; a/w ↑TNF- $\alpha$  levels
- Pityriasis lichenoides chronica (PLC)
  - Widespread, scaly, red-brown, scaly papules and plaques
  - Resolves w/ **hypopigmentation**
  - Persists longer than PLEVA
  - Adults: PLC > PLEVA

### Histology

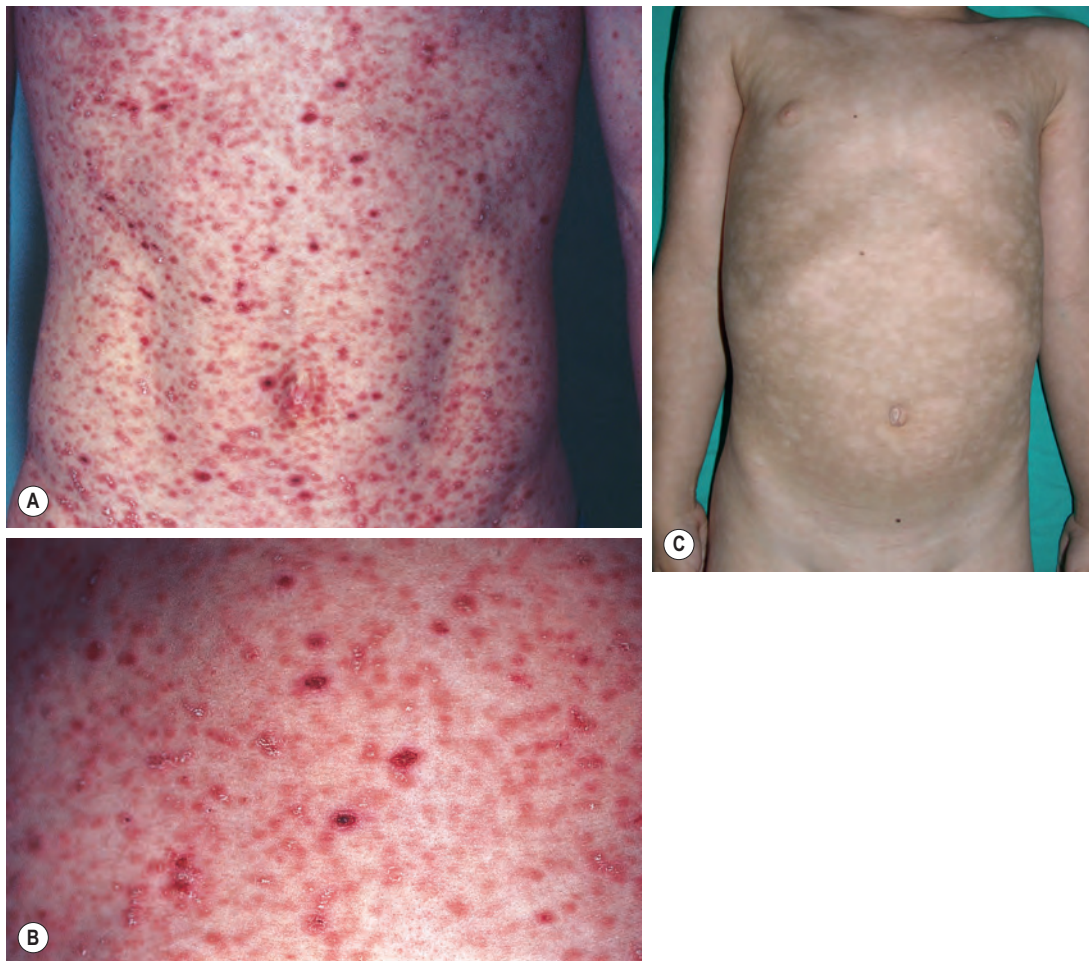
- **PLEVA: Parakeratosis, Lichenoid infiltrate, Extravasation of erythrocytes, V-shaped dermal lymphocytic infiltrate, Acute epidermal changes (dyskeratosis, ulceration, neutrophilic scale crust)**
- **PLC:** similar changes as PLEVA, but **much more subtle** – mild parakeratosis, milder vacuolar interface w/ fewer necrotic keratinocytes, milder RBC extravasation, and less dermal inflammatory infiltrate; almost never ulcerates
- Both have **strict absence of eosinophils!**

### Treatment

- First line: topical steroids, phototherapy, and systemic antibiotics (erythromycin, azithromycin, and TCN)
- Severe forms: MTX, cyclosporine, and IVIG

### Additional boards factoids

- Distribution is the best predictor for speed of disease resolution: **diffuse distribution is fastest to resolve**



**Figure 3-10.** (A) The polymorphic eruption of pityriasis lichenoides; note the mixture of acute (crusted) and chronic (scaly) lesions. (B) Higher power of (A). (C) Postinflammatory hypopigmentation associated with pityriasis lichenoides. Courtesy of A. Torrelo, MD (From Schachner LA, Hansen RC. *Pediatric Dermatology*, 4th ed. Elsevier. 2011.)



(average of 11 months) > central distribution > peripheral distribution (slowest resolution; average of 33 months)

- CD8+ T-cells predominate within infiltrate → helps distinguish from majority of other conditions in DDx

## Fixed drug eruption (FDE)

### Pathogenesis

- Most common causative meds:
  - Sulfonamides (75% of cases; #1 cause on **genitalia**)
  - NSAIDs (especially **naproxen** and other pyrazolone derivatives), predilection for **lips**
  - TCNs
  - Phenolphthalein (previously in **laxatives**; now less common because it has been removed)
  - Others: barbiturates, ASA, OCPs, and carbamazepine
- Non-pigmented FDE (clinical variant)
  - Pseudoephedrine (classic cause)
  - Others: NSAIDs, acetaminophen, and tetrahydrozoline (eye drops)

### Clinical features

- Most commonly affects **oral and genital mucosa** (#1 sites), face, and hands/feet
- **Initial episode:** develops 1–2 weeks after administration of causative drug
- **Subsequent episodes:** eruption recurs at same site **very rapidly** after reexposure (30 min to 8 hrs)
- **If meds are continued may → generalized FDE**
  - Generalized FDE may have mucosal involvement (difficult to distinguish from EM or SJS)
- Well-demarcated, edematous plaques w/ erythematous-violaceous hue
- Epidermal damage from interface reaction commonly leads to **central dusky hue, bulla, or erosion**
- Lesions self-resolve over 1–2 weeks, w/ prominent **postinflammatory hyperpigmentation**
- Clinical variants:
  - Non-pigmenting FDE
    - Most commonly due to **pseudoephedrine**
    - Very large, tender, “juicy red” plaques
  - Linear FDE: sometimes confused w/ linear lichen planus
  - Vulvar FDE: symmetrical erosive vulvitis on labia minora/majora and perineum
  - Generalized bullous FDE (GBFDE): significant overlap with SJS/TEN

### Histopathology

- EM-like **vacuolar interface** changes w/ scattered apoptotic keratinocytes in all layers of epidermis, moderately brisk superficial to mid dermal perivascular lymphohistiocytic infiltrate w/ **admixed eosinophils and neutrophils**, ↑↑**dermal melanophages** within papillary and reticular dermis (deeper than other interface processes)
  - vs. EM: “dirtier” inflammatory infiltrate (admixed eosinophils and neutrophils), deeper pigment deposition

- vs. SJS/TEN: ↑inflammation, ↑lymphocyte exocytosis, ↓necrosis, and ↑pigment incontinence

### Laboratory testing

- Patch testing **within a site of prior involvement** may be used to identify culprit med

### Prognosis/clinical course

- Benign; self-resolves in days to a few weeks if causative med is discontinued
- Exception: GBFDE may have mortality rate comparable to SJS/TEN (up to 22%)

### Additional boards factoids

- Occasionally, a “refractory period” after drug exposure occurs → thus, FDE does not necessarily occur every time implicated med is administered

## Graft versus host disease (GVHD)

### Epidemiology

- Frequent (>50%) complication of **allogeneic hematopoietic stem cell transplants (HSCT)** → severe skin disease and ↑mortality
- Less commonly occurs in setting of:
  - Transfusion of non-irradiated blood products to immunocompromised hosts
  - Maternal-fetal transmission
  - Solid organ transplantation (**small intestine** > liver > kidney > heart)
- Single **most important predictor** of developing GVHD after HSCT is **HLA compatibility**
  - ↑frequency of GVHD largely due to increasing use of matched **unrelated** donor (MUD) transplants over past few decades → MUD transplants have ↑rate of minor HLA mismatch compared to matched related donors
- Other risk factors for GVHD:
  - Female donor (especially multiparous women) w/ male recipient
  - Older age
  - Stem cell source
    - Risk of GVHD: **peripheral blood (PB-HSCT)** > bone marrow > cord blood
      - ◆ ↑popularity of PB-HSCTs in USA due to ease of collection; but must consider GVHD risk
  - Myeloablative preconditioning regimen (↑risk of acute GVHD due to damage to host tissues)
    - Many centers now performing non-myeloablative/reduced-intensity conditioning regimens to ↓toxicities → older people are able to tolerate transplants better nowadays
      - ◆ Non-myeloablative regimens may ↓risk of acute GVHD, but may also delay the onset to beyond the classic ≤100 day period → ↑incidence of “delayed-onset acute GVHD”
- Risk of developing GVHD in HSCT recipients:
  - HLA-matched: 40%
  - HLA-mismatched: 60%–70%
- Skin is most commonly affected organ in all forms of GVHD

### Pathogenesis

- Acute GVHD:
  - HSCT conditioning regimen damages host tissues
    - activation of host antigen presenting cells (APCs)
    - host APCs bind altered host proteins/neo-antigens
    - donor lymphocytes recognize altered host protein-APC complex → **donor lymphocytes proliferate and target host tissue** in skin, GI tract, and liver
- Chronic GVHD:
  - Molecular pathogenesis still unclear
  - May involve interaction of B- and T-cells
    - Rituximab (anti-CD20 antibody) helpful in some cases of chronic GVHD

### Clinical features

- Acute GVHD:
  - Traditionally defined as starting within **first 100 days** after transplant
    - Time period now felt to be arbitrary and not essential for diagnosis
  - Typically starts 2–6 weeks (**peak at day 30**) after HSCT
  - Initially p/w morbilliform eruption
    - First sites affected: **acral sites** (hands, feet, ears) and upper trunk
    - Early clues to diagnosis:
      - ◆ **Acral erythema**
      - ◆ **Violaceous hue on ear**
      - ◆ **Follicular/peri-ecrine erythema** (darker punctate lesions help distinguish from simple morbilliform eruptions)
  - Rash may progress to confluent erythematous plaques (SJS/TEN-like)
  - **GI tract and liver involvement** usually accompany skin findings
  - Clinical staging based on three factors:
    - Skin: severity assessed by % BSA
    - GI: severity assessed by **volume of diarrhea** (and severe abdominal pain)
    - Liver: severity assessed by degree of **bilirubin** elevation
- Chronic GVHD:
  - Traditionally defined as **starting ≥100 days** (average: 120 days) after transplant
    - Time period is now felt to be arbitrary and not essential for diagnosis
  - Preceded by acute GVHD in 50%
    - Occurs *de novo* in 50%
  - Chronic GVHD affects a greater variety of organ systems (nearly any organ)
  - The old terms “lichenoid” and “sclerodermoid” GVHD are no longer the preferred terms
    - Currently favored terms: “non-sclerotic GVHD” and “sclerotic GVHD”
  - Non-sclerotic cGVHD:
    - Often, but not always, precedes sclerotic cGVHD phase
    - Most common presentation is **lichenoid eruption** (80% of cases of cGVHD): coalescent, slightly scaly,



**Figure 3-11.** Chronic graft-versus-host disease (GVHD). Epidermal GVHD characterized by lichen planus-like changes on the posterior surface of the neck and upper aspect of the back. (From J Amer Acad Dermatol 2012 Apr;66(4):515.e1–e18; quiz 533–4. doi: 10.1016/j.jaad.2011.11.960. Graft-versus-host disease: part I. Pathogenesis and clinical manifestations of graft-versus-host disease. Hymes SR1, Alousi AM, Cowen EW. Elsevier. 2012)

violaceous-to-pink papules arranged in reticulate pattern (Fig. 3-11)

- ◆ Most common sites: dorsal hands/feet, forearms, and trunk
- Other morphologies of non-sclerotic cGVHD: **atopic dermatitis-like** (recently reported), psoriasiform, poikilodermatous, lupus-like, and keratosis pilaris-like
- **Sclerotic cGVHD**: encompasses multiple morphologies, favor areas of pressure
  - Lichen sclerosis-like
  - **Sclerodermoid/morphea-like** plaques
    - ◆ Unlike true scleroderma, the distribution is more patchy and lacks classic features of scleroderma (bird facies, puffy/indurated hands, and sclerodactyly)
  - Eosinophilic fasciitis-like

### Histopathology

- Acute GVHD: **basal vacuolar interface**, +/- keratinocyte necrosis (seen only in grade 2 and higher), sparse superficial perivascular lymphohistiocytic infiltrate
  - **Apoptotic cells in adnexal structures** (hair follicles and sweat ducts): very helpful clue to distinguish from simple drug eruptions!
  - Background of **epidermal dysmaturation** (resembles Bowenoid AK or chemotherapy effect): almost always present, useful clue

- Chronic GVHD: variable; the two most common patterns are:
  - **Lichenoid**: moderately dense perivascular to band-like lymphohistiocytic infiltrate w/ vacuolar or lichenoid interface changes and keratinocyte apoptosis; degree of lichenoid inflammation is typically less dense than in classic LP
  - **Sclerotic**: dermal sclerosis, +/- subcutaneous and fascial fibrosis, may see overlying vacuolar or lichenoid interface

#### Laboratory testing

- Acute GVHD: **bilirubin and diarrhea** volume
- Chronic GVHD: **MRI** can detect fasciitis (may eliminate need for fascial biopsy)

#### Treatment

- Prophylaxis improves survival
  - Most common prophylactic regimens: MTX + cyclosporine or tacrolimus
- Acute GVHD:
  - Limited GVHD (skin only): topical steroids, TCIs, and phototherapy
  - Most cases (skin + internal involvement): **systemic corticosteroids are first line** treatment (added to existing immunosuppressive regimen)
    - Systemic steroids achieve durable response in only 50% of patients
    - **Mortality rate for steroid-refractory cases = 70%**
- Chronic GVHD
  - Very difficult to treat
  - First line: topical + systemic corticosteroids added to immunosuppressive regimen
    - Only 50% respond
  - Second line: no option shown to be reliably effective
    - ECP, PUVA +/- isotretinoin, imatinib, and mTOR inhibitors

#### Prognosis/clinical course

- Acute GVHD: mortality = 30%–50% if moderate-severe disease (70% if steroid refractory)
- Chronic GVHD: most common cause of death is infection

#### Additional boards factoids

- Maraviroc (CCR5 inhibitor) decreases incidence of visceral GVHD by blocking CCR5-mediated CD8+ T-cell recruitment to liver and gut → may be useful for patients at high risk for GVHD
  - Does not ↓ incidence of skin GVHD

## Lichenoid interface dermatitis

### Lichen planus (LP)

#### Epidemiology

- Cutaneous LP affects up to 1% of adults; oral LP affects 4% of adults
- Most common in **middle aged adults** (peak onset: 40–50 yo); F > M

#### Pathogenesis

- **Various triggers** (viral, contact allergens, drugs, or idiopathic) → basal keratinocytes express altered self-antigens on cell surface → T-cells target basal keratinocytes → lower level (basal) keratinocyte apoptosis
  - Viral
    - **Hepatitis C virus**
      - ◆ Implicated in subset of **oral ulcerative/erosive LP**
      - ◆ Meta-analysis supported association with LP in selected regions only (Asia, South America, Europe, Middle East countries), but failed to detect an association in North America
    - Hepatitis B (vaccine): a/w oral LP, and bullous LP in children (an otherwise uncommon presentation)
  - Contact allergens (**mercury amalgam**, copper, and gold)
    - a/w oral LP
    - **95% improve** w/ removal of sensitizing metal
    - Even w/ negative patch test, 75% clear when metal is removed (may be related to irritant effects)
  - Drugs
    - Most common: **HCTZ, β-blockers, ACE inhibitors, antimalarials, gold salts, TNF-α inhibitors, NSAIDs, penicillamine, and quinidine**

#### Clinical features

- Inflammatory disease of the skin, hair, nails, and mucous membranes
- **Pruritic, Purple-violaceous Polygonal, flat-topped Papules**
  - Papules may be umbilicated
  - **Wickham's striae** and small grey-white puncta
  - **Koebnerization** very common
- Most common sites: **oral mucosa (#1 site), ventral wrists/forearms, dorsal hands, shins, genitalia, presacral area, and neck**
  - **Oral mucosa involved in 75% of all cases** (often the only site of involvement); **only 10% of patients who have oral LP subsequently develop cutaneous LP**
- Although LP is pruritic, rarely see excoriations or impetiginization
- Multiple clinical variants (**Table 3-5**)

#### Histopathology

- All clinical variants have similar histology
- Classic features: orthohyperkeratosis, **wedge-shaped hypergranulosis**, irregular acanthosis w/ "saw-toothed" rete ridges, vacuolar degeneration of the basal layer, **apoptotic keratinocytes confined to the basal layer** of epidermis with some falling into superficial dermis (cytoid/civatte/colloid bodies), and superficial dermal band-like ("lichenoid") lymphocytic infiltrate
- Lacks eosinophils
  - **Exceptions**: drug-induced LP, hypertrophic LP (recent study found frequent eosinophils in hypertrophic LP)
- Lacks parakeratosis
  - **Exceptions**: drug-induced LP and oral LP

**Table 3-5.** Key Features of Lichen Planus Variants

Acute (exanthematous) LP	Rapid onset of disseminated lesions; heals with PIH; rapidly self-resolves (3–9 mos)
Actinic LP	Most common in <b>Middle Eastern and Indian patients</b> (also Africans); young adults or children; onset in spring or summer on <b>sun-exposed sites</b> (face, forehead > dorsal UE, neck, intertriginous sites); comprised of red-brown annular plaques or melasma-like patches (less common)
Annular LP	Usually asymptomatic; annular plaques with raised violaceous-white edge with central clearing; resembles GA but is scaly; <b>axilla</b> is most common site, followed by <b>penis</b>
Atrophic LP	May represent resolving phase of LP with centrally depressed/atrophic, hyperpigmented area; clinically resembles early morphea or LS&A; legs most common site
Bullous LP	Blisters develop on longstanding LP lesions due to extensive epidermal damage ( <b>expanded Max-Joseph spaces</b> )
Drug-induced LP	In comparison to idiopathic LP: <b>patients typically 10 yrs older</b> (mid 60s); often spares “classic LP sites;” lesions <b>more generalized</b> and more eczematous or psoriasiform than classic morphology; <b>Wickham’s striae absent; frequently photodistributed</b> (esp HCTZ); <b>spares mucous membranes</b> ; histology: like LP but frequently has parakeratosis, deeper infiltrate, <b>eosinophils</b> , apoptotic keratinocytes in higher levels of epidermis; average latency period of 12 mos; delayed resolution (months)
Genital LP	Men: <b>annular LP</b> on glans penis Women: vulvar LP is most commonly <b>erosive</b> and 70% have concomitant vaginal involvement; often a/w oral involvement (“ <b>vulvovaginal-gingival syndrome</b> ,” protracted course with scarring, chronic pain, dyspareunia, and ↑ nail involvement)
Hypertrophic LP (aka LP verrucosus)	Extremely pruritic, thick, scaly plaques; most commonly on dorsal feet and shins; symmetric; lasts longer (avg duration 6 yrs); may lead to <b>multiple KAs</b> or follicular-based <b>SCCs</b> ; biopsy may show many eosinophils
Inverse LP	<b>Axilla</b> > inguinal and inframammary folds > antecubital and popliteal fossae; <b>hyperpigmentation</b> usually present (thus may overlap with LP pigmentosus)
Linear LP	Refers to lesions that appear spontaneously (not due to koebnerization) in a <b>Blaschkoid</b> distribution; favors younger patients (20–30 yo); likely due to somatic mosaicism
Oral LP	Over half of patients with cutaneous LP have oral involvement • <b>Reticular LP: most common</b> ; lacy white raised linear lines; usually asymptomatic; most commonly on <b>bilateral buccal mucosa</b> > gingivae > tongue > lips • <b>Atrophic, erosive, and bullous oral LP</b> : more painful, F > M; must check for esophageal and genital involvement; may progress to SCC (1%–2%)
Nail LP	Seen in 10% of LP patients; usually affects several nails; classic findings = <b>longitudinal ridging, lateral thinning, fissuring, and dorsal pterygium</b> ; kids lack these other nail findings but may present as <b>20-nail dystrophy</b> (rare in adults)
LP/LE overlap	Acral sites with bullae, ulceration, nail loss, and pain; overlapping features of lupus and LP seen clinically and on H&E/DIF
Palmoplantar LP	Commonly ulcerative (esp on soles); occurs in 30–40 yo age group; extremely painful and recalcitrant to therapy; usually with typical LP elsewhere
LP Pemphigoides	Vesicobullous lesions occur anywhere on skin (most commonly on uninvolved skin) due to <b>circulating IgG antibodies against BPAG2</b> (180 kD antigen, type XVII collagen); occurs weeks to months after onset of LP; pathogenesis: LP damages epidermis → exposes hidden antigens that are recognized by T-cells
LP Pigmentosus	<b>Skin types 3 and 4</b> ; brown or grey-brown macules on <b>sun-exposed face, neck, and flexures</b> ; lacks preceding erythema; evolves into reticulate hyperpigmented patches; classic LP lesions in only 20%; occurs later in life (30–40 yo) than ashy dermatosis (childhood to late 20s)
Lichen planopilaris (LPP)	<b>Perifollicular hyperkeratosis</b> with narrow violaceous rim on scalp (> other hair-bearing areas); <b>frontal fibrosing alopecia</b> : variant in elderly women along the frontal hairline
Graham-Little-Piccardi-Lasseur syndrome	Variant of LPP; classic triad = <b>non-scarring pubic and axillary hair loss</b> w/disseminated spiny <b>follicular papules</b> (KP-like), cutaneous or mucosal LP, and scarring <b>alopecia</b> on scalp

- Dyskeratotic keratinocytes are not present in higher levels of epidermis (spinous and granular layers) → differentiates from EM, FDE, and SJS/TEN (all have suprabasilar keratinocyte apoptosis)
  - **Exceptions:** drug-induced LP
- Deep dermal and peri-ecrine/perifollicular inflammation is not seen → differentiates from DLE and lichen striatus
  - **Exceptions:** drug-induced LP
- Minimal lymphocyte exocytosis (vs lichen striatus and PLEVA/PLC)
- DIF: “shaggy” fibrinogen along BMZ; colloid bodies stain with IgM (>IgA, IgG, C3)

#### Laboratory testing

- Patch testing to metals in patients w/ oral LP may be helpful

#### Treatment

- First, rule out lichenoid drug eruption (biopsy **NOT** a reliable distinguishing test → need careful drug history)
  - Lichenoid drug eruptions may persist for many months after drug discontinuation
- Once drug-induced LP has been ruled out, there are multiple treatment options:
  - **Corticosteroids (first line)**: topical, intralesional (good for hypertrophic LP), and systemic (for more severe forms)
  - TCIs: very effective for oral LP, but some experts are concerned about theoretical ↑SCC risk in oral LP
  - MTX: useful for generalized LP (>90% response rate)
  - Acitretin: effective in recalcitrant LP (64% have significant improvement)
  - Metronidazole: generalized LP (79% effective)



- Hydroxychloroquine: mainly used for LPP/frontal fibrosing alopecia
- Oral cyclosporine (recalcitrant cases)
- Phototherapy (UVB, UVA1, and PUVA)

#### Prognosis/clinical course

- Duration depends on type of LP variant
- **Most forms of LP resolve in 1–2 years** (60% by 1 year)
- **Oral** (especially ulcerative), **hypertrophic**, and **nail LP** tend to **persist**
  - Ulcerative oral LP very rarely resolves
  - Conjunctival and esophageal involvement are particularly worrisome
- ↑**SCC risk** in hypertrophic LP, oral (ulcerative type), and vulvovaginal LP

### Keratosis lichenoides chronica (KLC)

- Symmetric eruption on **extremities and trunk** comprised of **violaceous keratotic papules** coalescing into plaques w/ **linear to reticular** arrangement
- Classic clue: greasy, seborrheic-like centrofacial plaques
- Nails and scalp may be involved
- Typically chronic and progressive; no effective treatment
- Histologic and DIF findings are identical to LP

### Erythema dyschromicum perstans (ashy dermatosis, EDP)

- Asymptomatic, symmetric eruption of upper trunk, neck, and proximal extremities
- Preferentially affects **Latin Americans**
- Characterized by slow onset of **slate grey-brown** or grey-blue, oval macules and patches w/ erythematous rim
- Histology: subtle basal vacuolar change (usually only discernable at active inflammatory edge), **numerous dermal melanophages**, +/- band-like dermal lymphocytic infiltrate (sparse)
- DIF identical to LP
- Course: 70% of kids resolve within 2–3 years; adults typically more persistent
- Treatment: **clofazamine (ToC)**, dapsone, and LP treatments

### Lichenoid keratosis (BLK and LP-like keratosis)

- 85% occur between 35–65 years of age; F > M
- Usually due to inflammation of a lentigo, SK or AK
- Solitary, **pink or red-brown**, scaly, 0.5–1.5 cm plaques; lesions often confused for BCC
- Most common sites: **forearm**, **upper chest** > shins (women), and other sun damaged sites
- Histology: similar to LP, but often has **eosinophils**, **spongiosis**, **parakeratosis**, and less wedge-shaped hypergranulosis than LP
- DIF: Like LP
- No treatment necessary
- Caution: Elston showed that up to 1%–2% of “BLKs” may actually demonstrate regressing melanoma in situ on deeper sections!

### Lichen nitidus

- More common in **children and young adults**
- Multiple/grouped **pinpoint, uniform**, discrete, shiny, flat-topped or umbilicated, flesh-colored papules (Fig. 3-12)
  - Tend to be hypopigmented in dark skinned patients
  - **Koebnerization** common
- Favored sites: **genitalia**, **lower abdomen**, dorsal hands, flexor wrists, and inner thighs
  - Oral, nail, and palm/sole involvement uncommon
- Histology: classic “**ball and claw**” appearance
  - Well circumscribed, superficial dermal inflammatory nodule comprised of **lymphocytes, histiocytes, and giant cells** confined between two to three rete ridges; inflammatory infiltrate is surrounded by hyperplastic epidermal rete ridges that “clasp the dermal infiltrate”
  - Infiltrate is more “mixed” than LP (giant cells and CD1a+ Langerhans cells)
  - **Interface changes** (vacuolar-lichenoid)
  - **Atrophic overlying epidermis** w/ loss of granular layer +/- parakeratotic cap
- Majority (60%–70%) resolve spontaneously within 1 year
- Treatment often just symptomatic: topical steroids, TCIs, and phototherapy
- DDx:
  - **Lichen spinulosus**: follicular hyperkeratotic papules w/ **central keratotic spine** on neck, buttocks, abdomen, and upper arms
  - **Disseminate and recurrent infundibofolliculitis**: pruritic follicular-based eruption of **trunk and proximal extremities**; almost exclusively affects young, healthy black adults, often hx of atopic dermatitis; worsened by hot and humid environments; Rx = UVR or oral retinoids

### Lichen striatus

- F > M (average age = 4 yo)
- 50% of affected children are atopic



**Figure 3-12.** Isomorphic phenomenon in child with lichen nitidus. (From William L. Weston, Alfred T. Lane and Joseph G. Morelli. Color Textbook of Pediatric Dermatology. Elsevier: Mosby. 2007.)



- ↑incidence in spring and summer
- Typically asymptomatic 2–4 mm pink or hypopigmented scaly papules, **linear/Blaschkoid** distribution
  - **Extremities** >> face, trunk, buttocks
  - **Nail dystrophy** may occur if a digit is affected
- Treatments: topical steroids and TCIs
- Resolves spontaneously in 3–24 months

## Lichen sclerosus (LS, LS&A, and balanitis xerotica obliterans)

### Epidemiology

- F >> M, whites > non-whites
- Any age, but has **bimodal** peaks:
  - Major peak = 40–50 yo **post-menopausal females**
  - Second peak = prepubertal girls (8–13 yo)
- a/w autoimmune diseases (especially in women)
  - Most common: **autoimmune thyroid** disease (15%)
  - Others: pernicious anemia, localized scleroderma/morphea (6%), psoriasis, and vitiligo
- Most commonly affects male and female **anogenital region** (85%)
- Extragenital LS&A accounts for only 15%
- Male penile involvement = balanitis xerotica obliterans (BXO)
  - Common cause of **phimosis**

### Pathogenesis

- Unclear, but thought to be genetic predisposition and associated with **HLA-DQ7**
- 80% of patients have circulating **IgG autoantibodies against ECM-1**
  - ECM-1 = glycoprotein involved in regulation of BMZ integrity, collagen fibril assembly and other functions
- Hormonal factors: predominance in postmenopausal women, resolution in pregnancy, and ↑OCP use in pts

### Clinical features

- Classic lesions: **sclerotic, ivory-white**, atrophic, and flat-topped papules coalescing into plaques
  - **Follicular plugging** more prominent in extragenital LS&A
- **Genital LS&A is usually symptomatic** (itching, pain, and burning), whereas extragenital LS&A is typically asymptomatic
- Unlike LP, LS&A very rarely affects oral cavity or vagina
- **Genital LS&A (85% of cases):**
  - Most commonly affects vulvar and perianal area with classic **“figure of 8”** pattern in women (rarely see perianal involvement in men)
  - Pruritus and/or soreness is typical (often severe) → dysuria, **constipation (especially in kids)**; related to pain with defecation), dyspareunia, and discharge
  - Disease evolution: starts as well demarcated, thin erythematous plaques that may have focal superficial erosions → **epidermal atrophy, dermal scarring, hypopigmentation**, dermal hemorrhage/bruising, and fissures → **fusion of labia minora to majora, obliteration of clitoral hood**, and narrowing of vaginal introitus

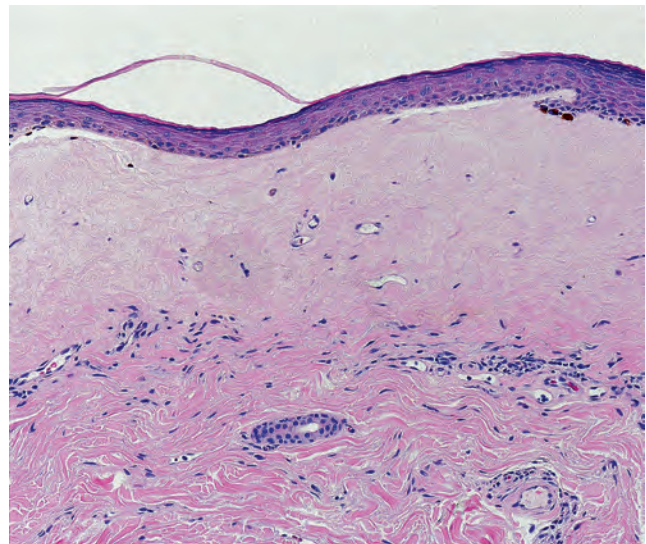
- Males: **glans penis** (most commonly), but also prepuce and coronal sulcus with atrophic ivory plaques, scars, and erosions → can develop **phimosis** if uncircumcised
- **Purpuric/ecchymotic** areas in anogenital LS&A are often misdiagnosed as sexual abuse
- ↑**risk of SCC** in patients w/ genital LS&A (5% risk)
- Koebnerization possible
- **Extragenital LS&A (15% of cases):**
  - Usually asymptomatic
  - Most common sites: **upper trunk/neck**, proximal upper extremities, and flexor wrists
  - Disease evolution: begins as polygonal blue-white shiny papules → coalesce into sclerotic plaques with **ivory white** color → **follicular plugging**, telangiectasias, and bruising

### Histopathology (Fig. 3-13)

- Compact orthohyperkeratosis, follicular plugging, epidermal atrophy with mild vacuolar interface changes, and **papillary dermal edema or homogenization** w/ underlying **lichenoid lymphocytic infiltrate**
  - Mnemonic: **“Red, white, and blue sign”** = orthohyperkeratotic stratum corneum (**pink-red**), hyalinized/edematous papillary dermis (**pale/white**), and band-like lymphocytic infiltrate (**blue band**)

### Treatment

- First line: **ultra-potent topical steroids** (e.g., clobetasol) in adults and children
  - Safe even if used long-term
- **Circumcision is ToC in males w/ phimosis**
- Second line: TCIs
  - Theoretical risk of ↑SCC and HPV reactivation
- Refractory cases: PUVA/UVA1, systemic immunosuppressants



**Figure 3-13.** Lichen sclerosus. (From Rapini R. *Practical Dermatopathology*, 1st Ed. Elsevier. 2007)

*Prognosis/clinical course*

- May resolve spontaneously in childhood (especially in puberty for girls), but relapsing course in adults
- Up to 50% of all vulvar SCCs occur in setting of LS&A!!!
- Estimated 5% risk of genital LS&A progressing to SCC
  - Vulvar SCC in setting of LS&A has recently been shown to be distinct from HPV-induced vulvar SCC
    - Much higher risk of developing invasive disease (33% vs 5.7%)
    - SCC due to LS&A may be difficult to diagnose histologically because it is well differentiated → mistaken for reactive epidermal hyperplasia
- Up to 55% of penile SCC is a/w LS&A

*Additional boards factoids*

- ECM-1 is mutated in lipid proteinosis
- Randomized trials of vulvar LS have shown:
  - Superiority of clobetasol over TCIs and UVA-1
  - Equivalence of mometasone and clobetasol

## 3.4 BLISTERING DISEASES

**Pemphigus disease family**

- In normal tissue, epithelial cells are held together by two major types of junctions:
  - **Adherens junctions:** classic cadherins (calcium-dependent adherins; E-, P-, and N-cadherins) are transmembrane proteins that bind to the armadillo family intracytoplasmic plaque proteins ( $\beta$ -catenin, plakoglobin) → bind to intracytoplasmic  $\alpha$ -catenin → anchor bundles of actin microfilaments → mediate **quick but weak cellular adhesion**
  - **Desmosomes:** desmosomal cadherins (calcium-dependent adherins; desmogleins and desmocollins) are transmembrane proteins that bind to the armadillo family intracytoplasmic plaque proteins (plakophilin and plakoglobin) → bind to intracytoplasmic **plakins** (desmoplakin 1 and 2, BPAG1, plectin, envoplakin, and periplakin) → anchors keratin intermediate filaments → mediate **slow but strong cellular adhesion** (**Box 3-1**)
- In various forms of pemphigus, autoantibodies (IgG or IgA) interfere w/ various proteins in **desmosomal** complex → loss of connection between adjacent epithelial cells → acantholysis at various mucocutaneous sites/levels
  - Desmoglein 1: expressed in **all levels** of the epidermis (**top > bottom**)
    - Dsg1 can compensate for Dsg3 loss in skin → therefore, if only Dsg3 is targeted (as in *P. Vulgaris*), the skin remains intact
    - Dsg1 has no significant role in mucosal epithelial adhesion → CANNOT compensate for Dsg3 loss in

**Box 3-1. Boards Factoid**

**Plakoglobin** is an armadillo protein that is present in **both desmosomes and adherens junctions**; it can substitute for  $\beta$ -catenin in the latter

mucosa → if Dsg3 function is lost (as in *P. Vulgaris*), mucosal blisters ensue

- Desmoglein 3: expressed mostly in **lower portion** of epidermis and **throughout mucosal epithelium**
  - Dsg3 CANNOT compensate for Dsg1 loss in superficial epidermis → if Dsg1 is targeted (as in *P. Foliaceus* and mucocutaneous *P. Vulgaris*), the skin develops blisters
  - Dsg3 is the major desmoglein involved in **mucosal epithelial adhesion**
- Desmoglein 4: important role in **hair follicles**
  - Dsg4 is mutated in autosomal recessive localized hypotrichosis and also **autosomal recessive monilethrix**

**Pemphigus vulgaris (PV)***Epidemiology*

- **Most common form of pemphigus** in most of world (PV: PF ~3 : 1)
- M = F; 50–60 yo
- **Jewish ancestry** a/w 10x ↑ incidence
- May be a/w other autoimmune diseases: **myasthenia gravis, thymoma, and autoimmune thyroiditis**

*Pathogenesis*

- Autoantibodies to **Dsg3** (mucosal-dominant pemphigus) or both **Dsg1 and Dsg3** (mucocutaneous pemphigus)
- In **neonates of mothers w/ PV**, maternal IgG autoantibodies against Dsg3 cross placenta → transient blistering in infant
  - Does not occur in mothers with PF, because neonatal skin has same Dsg expression pattern as **adult mucosa** (Dsg1 loss can be compensated for by Dsg3 expression)

*Clinical features*

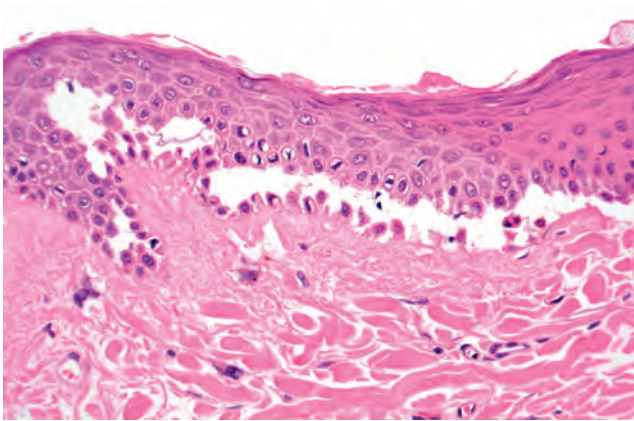
- All patients have painful **oral erosions** (most common sites = **buccal** and **palatine** mucosa) w/ irregular borders and different shapes and sizes
  - Other sites: esophagus (sloughing/cast formation), conjunctiva, nasal mucosa, vagina, penis, and anus
- **Skin involvement (50%)**: flaccid vesicles/bullae (**Fig. 3-14**), positive Nikolsky and Asboe-Hansen signs → bullae easily rupture, erode, and form crust
  - Heals without scarring
  - Widespread denudation may result in death from fluid imbalance or secondary infection
- **Pemphigus vegetans**: vegetative variant of PV affecting **intertriginous areas** (> scalp and face)
  - Reactive phenomenon to friction
  - Early lesions are flaccid pustules rather than vesicles → erosions → vegetative/papillomatous plaques

**Box 3-2. Boards Factoids**

- 1) Dsg1 is cleaved by *S. aureus* exfoliatins (bullous impetigo, SSSS)
- 2) Dsg1 mutation (AD) is present in striate PPK 1 (of note, desmoplakin is mutated in striate PPK 2, and keratin 1 in striate PPK 3; all are part of the desmosome complex)



**Figure 3-14.** Flaccid blisters and erosion as a result of a ruptured bulla. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-15.** Histology of pemphigus vulgaris. Blisters in the skin show suprabasilar acantholysis with a few acantholytic cells in the blister cavity. Attachment of the basal cells to the basement membrane via hemidesmosomes leads to the "tombstone" appearance. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Histology: PEH, intraepidermal eosinophilic abscesses, and suprabasilar acantholysis (often subtle)

#### Histopathology

- Eosinophilic spongiosis (earliest finding) → later, see classic findings of suprabasilar acantholysis without keratinocyte necrosis, "tombstoning" (vertically-oriented basilar keratinocytes attached to BMZ, but not surrounding keratinocytes), and individual rounded-up (acantholytic) keratinocytes within blister cavity (Fig. 3-15); hair follicles extensively involved
  - vs. Hailey-Hailey (the main histologic DDx): prominent acantholysis of hair follicles, ↑ eosinophils, lacks "dilapidated brick wall" appearance (i.e., lacks diffuse acantholysis in upper layers of epidermis), and lacks epidermal hyperplasia

#### Laboratory testing

- DIF: most reliable test (~100%); perilesional biopsy; assesses patient's skin for in vivo bound IgG; characteristic

#### Box 3-3. Boards Factoids

Best IIF Substrates for pemphigus variants:

PF: Guinea pig esophagus

PV: Monkey esophagus

PNP: Rat bladder

BP : salt split normal human skin

- intercellular "chicken wire" staining with IgG (100%) +/- C3; lower epidermis most strongly stained
- IIF: assesses patient's serum for circulating IgG autoantibodies (80%–90%); monkey esophagus is best substrate (Box 3-3); levels correlate w/ disease activity → useful for monitoring
- Immunoprecipitation and immunoblotting: detects target antigens of specific molecular weights via protein electrophoresis; distinguishes between pemphigus types more accurately than DIF or IIF
- ELISA: assesses patient's serum for circulating IgG autoantibodies (both Dsg1 and Dsg3); levels correlate w/ disease activity → useful for monitoring; can distinguish between pemphigus types

#### Treatment

- First line: oral steroids (1 mg/kg a day) + steroid-sparing immunosuppressive (azathioprine appears to be most effective)
  - TCNs + nicotinamide may be sufficient for very mild cases
- Second line: plasmapheresis useful for rapid control of severe disease; high dose IVIG and rituximab effective for recalcitrant disease
- Monitor treatment response with IIF or ELISA levels

#### Pemphigus foliaceus (PF)

- Second most common form of pemphigus\*; milder
  - \*Exceptions: Brazil (17:1 PF:PV), Tunisia (4:1), Finland (2:1)
- Important clinical variants:
  - Fogo selvagem: endemic variant of PF with identical clinical and histologic features; highest incidence in rural Brazilian towns within 10 miles of rivers rich in black flies (*Simulium* spp); affects children and young adults (vs middle aged to elderly in typical PF)
  - Pemphigus erythematosus (Senear-Usher syndrome): lupus/PF overlap; localized to malar region of face and other seborrheic areas; DIF shows intercellular pemphigus pattern + granular to linear IgG and C3 along BMZ (lupus pattern)
    - ANA+ in 30%
    - Rx: sun protection, steroids +/- dapsone
- Pathogenesis: autoantibodies to Dsg1 (IgG4 subclass)
- Clinical presentation:
  - Subacute onset of well-demarcated, transient, impetigo-like crusted erosions on an erythematous base
  - Favors seborrheic distribution (face, scalp, upper trunk) (Fig. 3-16)
  - Blisters are so superficial and fragile that usually only eroded/crusted lesions or plaques with "cornflake" scale are seen





**Figure 3-16.** Pemphigus foliaceus. Scaly, crusted erosions widely distributed on the back. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- (+) Nikolsky sign
- Lacks mucosal involvement
- Not severely ill; low mortality
- Histopathology: eosinophilic spongiosis (early) → subcorneal acantholysis (granular layer  $\gg$  midlevel epidermis) w/ acantholytic single cells in roof or floor of blister cavity; +/- neutrophils and eosinophils in blister cavity
  - PE, pemphigus erythematosus, SSSS, and bullous impetigo all show nearly identical findings on H&E
- DIF: same as PV, but upper epidermis most intensely stained
  - Unique exception: Senear-Usher syndrome shows intercellular pemphigus pattern + granular to linear IgG and C3 along BMZ (lupus pattern)
- IIF: same appearance as PV; guinea pig esophagus is best substrate (Box 3-3)
- Must differentiate from drug-induced PF and other pemphigus variants (Table 3-6)
- Rx: systemic steroids +/- dapsone (widespread disease); super potent topical steroids (localized disease)
- Like PV, may be a/w other autoimmune diseases

### Paraneoplastic pemphigus (PNP)

- Multisystemic, erosive, paraneoplastic syndrome a/w various underlying neoplasms (one third undiagnosed at time of PNP onset):
  - Non-Hodgkin's lymphoma (40%) > CLL (30%) > Castleman's disease (10% overall, #1 cause in children) > thymoma (6%), sarcoma (6%), and Waldenström's macroglobulinemia (6%)
- Autoantibodies against nearly all components of desmosome:
  - Entire plakins family: desmoplakin 1 and 3, BPAG1, plectin, periplakin, envoplakin, and A2ML1
  - Desmogleins: Dsg1 and Dsg3
- Mucosal involvement is severe:
  - Severe stomatitis w/ extension onto vermillion is the earliest, most common, and most persistent sign

**Table 3-6.** Pemphigus Variants

Pemphigus herpetiformis	Variant of PF (>PV) that clinically <b>resembles DH</b> ; p/w pruritic urticarial plaques and small, DH-like vesicles in herpetiform arrangement; Histopathology: <b>Minimal to no acantholysis</b> ; eosinophilic spongiosis and subcorneal pustules; DIF: same as PF; Antigen: <b>Dsg1</b> >Dsg3; chronic, but not severe; may evolve into classic PF (>PV)
IgA Pemphigus	Middle-aged to elderly; p/w pruritic flaccid vesicles/pustules in <b>annular/circinate pattern</b> with central crusting; most common on <b>axillae, groin</b> ; no mucosal involvement; no significant morbidity; DIF+ in 100%; IIF+ in 50%; <b>may be a/w IgA gammopathy</b> (and possibly multiple myeloma); <b>ToC = Dapsone</b> (#1; resolution within 48hrs), sulfapyridine, steroids. <b>SPD-type</b> : clinically and histologically indistinguishable from Sneddon-Wilkinson → need DIF/IIF; DIF shows intercellular IgA staining in upper epidermis; Target antigen = <b>Desmocollin 1</b> ; Histopathology: Subcorneal neutrophilic pustule; acantholysis not usually present. <b>Intraepidermal Neutrophilic type</b> : Characteristic "Sunflower-like" arrangement of vesicopustules; DIF: IgA intercellular staining throughout entire epidermis; Target antigen = <b>Dsg1/Dsg3</b> ; Histopathology: Suprabasilar neutrophilic pustule in lower-mid epidermis +/- mild acantholysis.
Drug-induced Pemphigus	Typically has <b>PF-like presentation</b> (4:1, PF:PV); most commonly induced by Thiol (sulfhydryl)-containing drugs (> non-thiols) <b>Thiols</b> (may cause acantholysis directly): <b>Penicillamine</b> (50%), <b>ACE-inhibitors</b> (captopril >enalapril, lisinopril), ARBs. <b>Non-thiol</b> (acantholysis via immune mechanisms, more likely to cause PV-like presentation); $\beta$ -lactams, gold, CCBs, $\beta$ -blockers, piroxicam, rifampin.

- Severe scarring conjunctivitis; esophageal, genital, and nasopharyngeal lesions also common
- Skin findings are polymorphous:
  - Most commonly pemphigus-like or lichenoid (most common chronic presentation)
    - Other presentations: pemphigoid-like, EM-like
  - Palms/soles frequently affected (unlike PV)
- Histopathology: polymorphous, just like the clinical presentation (**overlap between PV, LP, and EM findings**):
  - Suprabasilar acantholysis, vacuolar or lichenoid interface dermatitis w/ necrotic keratinocytes (not seen in PV), and far fewer eosinophils than PV
- DIF: IgG and C3 deposited in **intercellular spaces and linearly along BMZ**
- IIF shows same pattern using **rat bladder (best substrate)**
- Diagnostic gold standard: immunoprecipitation/immunoblotting (detects anti-plakin IgG) + anti-Dsg IgG by ELISA
- Treatment:
  - **Excision of benign neoplasms** (thymomas and localized Castleman's) → resolution within 6–18 months
  - PNP a/w **malignant processes** is highly recalcitrant
    - Attempt to treat underlying malignancy
    - Poor prognosis (up to 90% mortality rate)

- Most common causes of death = underlying **malignancy and bronchiolitis obliterans** (detect w/ PFTs  $\gg$  CT/X-ray)
- Symptomatic treatment: high dose steroids + steroid-sparing immunosuppressants

### Autoimmune subepidermal blistering diseases

- Subepidermal bullae result from damage to components of BMZ
  - Damage may be mediated by autoantibodies, mutated genes, or trauma
- Sites of damage: 1) basal keratinocyte (and its hemidesmosomal plaques); 2) lamina lucida; 3) lamina densa; and 4) sublamina densa
- Know the location and interactions of various components of BMZ (boards favorite!) (Fig. 3-17) and (Table 3-7)

### Bullous pemphigoid (BP, pemphigoid)

#### Epidemiology

- **Most common** autoimmune blistering disorder
- Usually **chronic**; may be a/w significant morbidity but usually **low mortality**
- **Elderly** (>60 yo, mean 75–81 yo) most commonly affected
  - Drug-induced BP commonly affects younger age groups

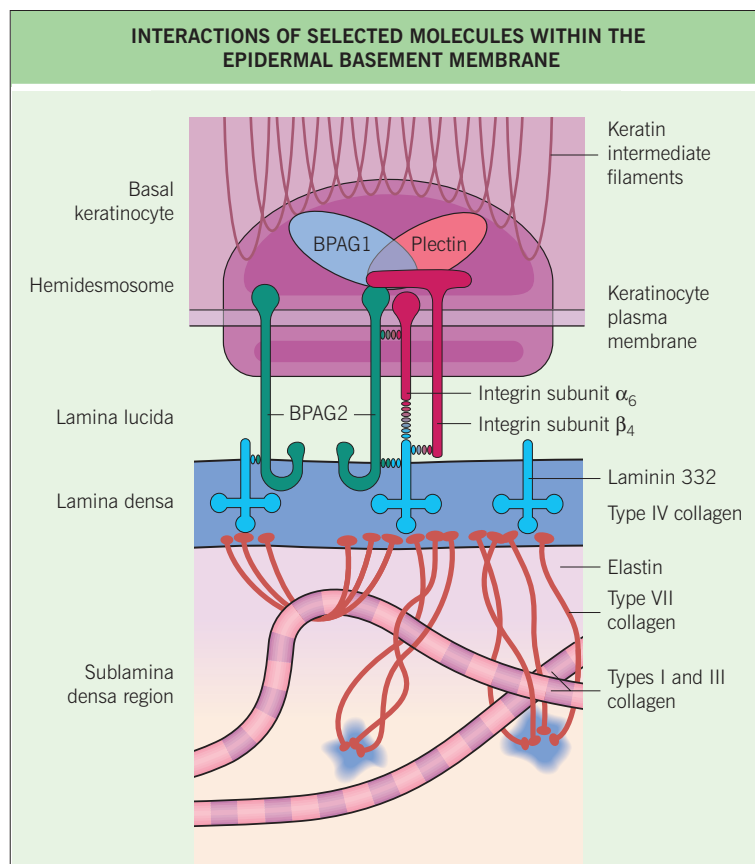
- Slight male predominance
- a/w HLA-DQB\*0301 (Caucasians)

#### Pathogenesis

- IgG (IgG1 and IgG4) autoantibodies bind **hemidesmosomal proteins**  $\rightarrow$  complement activation  $\rightarrow$  eosinophil and neutrophil recruitment to tissues  $\rightarrow$  release of matrix metalloproteinases, proteases, and neutrophil elastase  $\rightarrow$  degradation of ECM proteins  $\rightarrow$  subepidermal blister
- Most important target antigens:
  - **BP180 (BPAG2, type XVII collagen)**: 180 kD transmembrane protein; **primary mediator** of BP; main pathogenic target = non-collagenous NC16A domain
  - **BP230 (BPAG1)**: 230 kD cytoplasmic plaque protein belonging to **plakin** family; **not the primary mediator** of BP  $\rightarrow$  antibodies arise as secondary phenomenon ("epitope spreading")
- IgE a/w early urticarial phase of BP and IgE autoantibodies to type XVII collagen have been detected

#### Clinical features

- **Non-bullous phase (early)**: persistent, polymorphous eruption; may p/w isolated intense pruritus or **fixed urticarial papules/plaques** (often annular); usually affects **trunk, abdomen, and flexural extremities**
- **Bullous phase**: **tense**, fluid-filled vesicles/bullae (clear > blood tinged) arising on **urticarial background**; intense pruritus; **trunk, abdomen, and flexural extremities** most



**Figure 3-17.** Interactions of selected molecules within the epidermal basement membrane. These interactions promote epidermal adhesion and also play a key role in a number of dermatologic diseases. Important molecular interactions include those between: (1) plakin family members, BPAG1 and plectin, with keratin intermediate filaments; (2) the former with BPAG2 and integrin  $\alpha 6 \beta 4$  (specifically, the large cytoplasmic domain of integrin subunit  $\beta 4$ ); (3) the cytoplasmic domains of BPAG2 and integrin subunit  $\beta 4$ ; (4) the extracellular domains of BPAG2 and integrin subunit  $\alpha 6$  as well as laminin 332 (formerly laminin 5); (5) integrin  $\alpha 6 \beta 4$  in hemidesmosomes and laminin 332 in the lamina densa; (6) laminin 332 and type VII collagen and; (7) type VII collagen with type IV collagen, fibronectin, and type I collagen in the sublamina densa region. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Table 3-7.** Subepidermal Blistering Disease Characteristics

Disease	Antigen	Size (kDa)	DIF	Salt-Split Skin
Bullous pemphigoid	BPAG1 (plakin) <b>BPAG2 (collagen XVII)</b>	230 <b>180</b>	<b>Linear C3 and IgG</b> along BMZ in “n-serrated” pattern	Epidermal
Pemphigoid gestationis	BPAG2 (Collagen XVII)	180	<b>Linear C3 &gt; IgG</b> along BMZ	Epidermal
LABD	<b>LAD-1 (120kD)</b> cleaved portion of BPAG2 <b>LABD97 (97kD)</b> cleaved portion of LAD-1)	120→ <b>97</b>	Linear IgA +/-C3 along BMZ	Epidermal (IgA)
Mucous membrane pemphigoid (classic form)	BPAG2 ( <b>C-terminus</b> )	180	Linear IgG and C3 along BMZ	Epidermal (or both sides with stronger staining on epidermal side)
Ocular-predominant MMP	<b>β<sub>4</sub> integrin</b>	NA	Linear IgG and C3 along BMZ	Epidermal
Anti-epiligrin MMP	<b>Laminin 332</b>	400-440	Linear IgG and C3 along BMZ	Dermal
p200 pemphigoid	Laminin γ1	200	Linear IgG and C3 along BMZ	Dermal
p105 pemphigoid	NA	105	Linear IgG and C3 along BMZ	Dermal
EBA	<b>Type VII collagen</b> (anchoring fibrils)	290	<b>Linear IgG &gt; C3</b> along BMZ in “u-serrated” pattern	Dermal
Bullous SLE	<b>Type VII collagen</b> (anchoring fibrils)	290	<b>Granular to linear</b> staining w/ <b>multiple reactants</b> (IgG, IgA, IgM, C3)	Dermal
PCT	NA	NA	<b>Linear IgG (&gt;IgM), C3 and fibrinogen</b> along BMZ and <b>around superficial vessels</b>	Negative

**Table 3-8.** Pemphigoid Variants

Pemphigoid vegetans	Vegetative plaques in <b>intertriginous</b> areas
Infantile/childhood Pemphigoid	Frequently p/w <b>acral bullae</b> → generalizes; ↑ <b>facial/genital</b> involvement; clinically indistinguishable from childhood LABD/CBDC → need DIF/IIF
Pemphigoid nodularis	Clinically resembles prurigo nodularis; typically lacks bullae
Lichen Planus pemphigoides	<b>LP/BP overlap</b> syndrome w/circulating antibodies against BP180; p/w LP-like papules/plaques and tense bullae arising on skin unaffected by LP
Pemphigoid gestationis (gestational pemphigoid, herpes gestationis)	Abrupt onset; <b>any trimester (second and third most common)</b> , immediately <b>post-partum</b> , or a/w trophoblastic tumors ( <b>choriocarcinoma</b> , hydatidiform mole); starts as urticarial/vesicular plaques on trunk, abdomen, <b>umbilicus</b> → rapidly generalizes; <b>75% flare at time of delivery</b> ; <b>anti-HLA antibodies (~100%)</b> ; strongly a/w <b>HLA-DR3 (70%), DR4 (50%)</b> , or both (45%); DIF: <b>linear C3 (100%) &gt; linear IgG (30%)</b> ; IIF: only positive in 30%; <b>ELISA for BP180-NC16A</b> is best serum test; ↑risk of <b>premature delivery</b> and SGA neonates; <b>neonates may develop transient blistering</b> (10%); <b>recurs</b> in subsequent pregnancies; a/w <b>Graves’ disease</b> and anti-thyroid antibodies; Rx: systemic steroids
Localized pemphigoid	Pretibial, peristomal, vulvar, umbilical, distal portion of amputated limb (“stump pemphigoid”), radiotherapy sites, paralyzed limbs
Drug-induced pemphigoid	<b>Furosemide (#1), ACE inhibitors, cephalosporins, β-lactams, D-penicillamine</b> , Sulfasalazine, NSAIDs, neuroleptics, gold, SSKI, bumetanide, phototherapy Mnemonic: “ <b>F</b> at <b>A</b> bdomens <b>C</b> overed <b>B</b> y <b>P</b> emphigoid = <b>F</b> urosemide, <b>A</b> CE-inhibitors, <b>C</b> ephalosporins, <b>β</b> -lactams, <b>P</b> enicillamine”
Anti-p200 pemphigoid	Most often p/w classic BP eruption (>DH, eczematous presentations); head and mucous membranes more frequently involved; often <b>a/w psoriasis</b> ; target antigen: <b>laminin γ1</b> ; salt-split skin: IgG binding to <b>dermal</b> side
Anti-p105 pemphigoid	Extensive blistering and denudation on both mucous membranes and skin, resembling <b>SJS/TEN</b> (“p105 = <b>TEN</b> ”); target antigen: 105 kDa protein; salt-split skin: IgG binding to <b>dermal</b> side

common; bullae rupture to leave erosions and crusted areas; **oral involvement (10%–30%)** may occur, but much less common than PV; other mucosal sites less commonly affected; **peripheral eosinophilia (50%)**

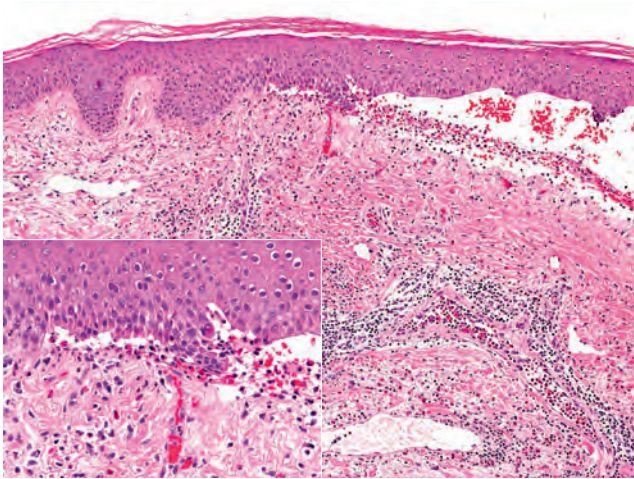
- **Pemphigoid variants:** Table 3-8

### Histopathology

- Urticarial phase: **eosinophilic spongiosis** w/ eosinophils lining up at DEJ and scattered in superficial dermis, vacuoles at DEJ (represents early blister formation)
- Bullous phase (Fig. 3-18) **subepidermal split** w/ numerous **eos** in blister cavity, dense dermal lymphoeosinophilic inflammation
  - May see **flame figures** at any phase

### Laboratory testing

- **DIF (most sensitive):** skin test for **in vivo** bound antibodies; substrate = biopsy from patient’s perilesional, uninvolved skin
  - **Linear C3 (n-serrated pattern) (~100%)** and **IgG (>90%)** located along DEJ
- **Salt-split skin DIF:** modified DIF study that allows for **localization** of **in vivo** bound antibodies
  - Technique: first use 1M NaCl to split the biopsied skin specimen at lamina lucida → examine w/ DIF for **in vivo** bound antibodies → determine which side of blister (roof vs. floor) the antibodies are bound to
  - Enables differentiation of BP (“**roof staining**”) from “**floor-staining**” blistering diseases (mainly EBA)



**Figure 3-18.** Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils, and mononuclear cells. Courtesy, Lorenzo Cerroni, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

#### Box 3.4. Serration Patterns in Subepidermal Blistering Diseases

n-serrated linear DIF pattern: BP, linear IgA

u-serrated linear DIF pattern: EBA **Bullus SLE**

- Examination of **serration pattern (n-serrated vs. u-serrated)** on standard DIF can be used in lieu of this technique (**Box 3-4**)
- **IIF** (60%–80% sensitive): **serum test** for circulating anti-BMZ IgG; **substrate = salt-split normal human skin (not patient's skin)**; allows for **localization** of antigens targeted by circulating autoantibodies
  - Serum from BP patients → **epidermal (roof) staining** (vs. EBA = dermal/floor staining)
  - IIF levels do **NOT** correlate well w/ BP disease activity (unlike IIF for PV)
- **ELISA** (80%–90% sensitive): **serum test** for detecting circulating antibodies to BP180 and BP230
  - ELISA levels (both IgG and IgE) correlate strongly w/ BP disease activity → useful for monitoring response to treatment

#### Treatment

- First line: **systemic steroids + steroid-sparing immunosuppressives** (MMF, MTX, azathioprine, and cyclophosphamide)
  - Newly-reported alternative: widespread superpotent topical steroids (high risk of skin atrophy)
- Other treatment options:
  - TCN class + nicotinamide (mild disease)
  - Dapsone (mucosal-predominant BP)
  - **Rituximab** (emerging utility; effective in recalcitrant cases)
  - IVIG, plasma exchange

#### Prognosis/clinical course

- Tends to be chronic, w/ significant morbidity and variably reported mortality (10%–40% in first year)
- ↑ELISA levels and/or **positive DIF** at time of therapy cessation → **high chance of relapse**



**Figure 3-19.** Scarring ocular disease in a patient with cicatricial pemphigoid. (From Callen JP, et al. *Dermatological Signs of Internal Disease* 4th ed. Elsevier. 2009)

### Mucous membrane pemphigoid (MMP, cicatricial pemphigoid)

#### Epidemiology

- Rare, chronic disease of **elderly** (60–80 yo)
- F > M

#### Pathogenesis

- Autoreactive IgG antibodies directed against various antigens in **anchoring filament zone** (vs hemidesmosomal plaque in conventional BP)
- Three well-defined subgroups:
  - **Anti-epiligrin MMP**: target = **laminin 332 (laminin 5, epiligrin)**; salt-split skin shows **dermal staining**; strongly a/w underlying **solid organ malignancy** (#1 = adenocarcinoma)
  - **Ocular MMP**: target =  **$\beta_4$  subunit** of  $\alpha_6\beta_4$  integrin; nearly exclusive ocular involvement
  - **Anti-BP antigen MMP**: target = **BP180 (C-terminus)**; skin and mucosal involvement

#### Clinical features

- Chronic disease characterized by predominant involvement of **mucosae (> skin)** w/ **scarring**; all mucosal sites susceptible, but **oral** (85%) and **conjunctival mucosa** are most common (**Fig. 3-19**)
  - **Oral (#1 site)**: gingiva, buccal mucosa, and palate (> tongue, lips); p/w erythema and erosions of gingiva (**desquamative gingivitis**), painful chronic erosions (especially palate), and rarely blisters
  - **Conjunctiva (#2 site)**: bilateral > unilateral; begins as non-specific conjunctivitis → subepithelial conjunctival fibrosis → **symblepharon** (adhesion of bulbar and palpebral conjunctivae), **trichiasis** (inward facing eyelashes), **entropion**, **ectropion**, and xerosis → trauma induces corneal neovascularization, ulceration, and **blindness**
  - **Other mucosal**: nasopharyngeal/upper aerodigestive tract (epistaxis and airway obstruction); laryngeal

(hoarseness, life-threatening stenosis); esophageal (dysphagia and strictures); anogenital (strictures and obliteration of orifices)

- **Skin involvement** (25%): fewer lesions, different distribution and morphology than conventional BP
  - Most common sites: **scalp/face/neck** and upper trunk
  - Erythematous plaques and recurrent blisters/erosions → heal w/ **atrophic scars** (not seen in BP)
- **Brunsting-Perry variant**: lesions limited to **head/neck** → **scarring alopecia**; no mucosal involvement

#### Histopathology

- Similar to BP, except has fewer eosinophils (mostly lymphocytes and plasma cells) and ↑dermal fibrosis/scarring

#### Laboratory testing

- DIF: **most reliable** test (80%–95% sensitive) → linear IgG, IgA, and/or C3 along BMZ
- IIF: only a minority (20%–30%) have detectable circulating antibodies (low titers)
- Salt-split skin: **epidermal (roof) staining in all forms of MMP, except anti-epiligrin (anti-laminin 332) MMP** (= dermal/floor staining)

#### Treatment

- Mild-moderate oropharyngeal and cutaneous disease: **dapsone** (first line; may also help in mild ocular disease) + potent topical/IL steroids; other options include:
  - TCNs + nicotinamide (ok for mild disease)
  - Short courses of oral steroids
- Severe or progressive ocular disease: **cyclophosphamide** (ToC) + systemic steroids or steroid-sparing **immunosuppressive** (MMF and azathioprine)
  - IVIG and biologic agents are other options for severe disease
  - Surgical correction of severe ocular scarring may only be attempted AFTER disease controlled!

#### Prognosis/clinical course

- Chronic, disfiguring, and blindness-inducing (most common concern); but rarely fatal

### Linear IgA bullous dermatosis/chronic bullous disease of childhood (LABD/CBDC)

- Rare autoimmune subepidermal blistering disease defined by linear IgA deposition along BMZ
- Affects elderly adults (average >60 yo; termed **LABD**) and preschool-aged children (average age: 4 yo; termed **CBDC**)
  - **Adult-onset LABD is typically drug-induced** → **vancomycin** (most common) > PCN/CSN, captopril (> other ACE inhibitors), NSAIDs > phenytoin, sulfonamides > many others (e.g., furosemide and lithium)
- Pathogenesis: **IgA autoantibodies** directed against two related antigens, both derived from BPAG2:
  - **LAD-1** (120 kD cleaved portion of BP180 antigen)
  - **LABD97** (97 kD cleaved portion of LAD-1)



**Figure 3-20.** Chronic bullous disease of childhood. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

- Clinical presentation
  - Tense vesicles/bullae and urticarial plaques in an **annular, polycyclic, or herpetiform** ("crown of jewels") arrangement (**Fig 3-20**)
  - Most common sites: flexures of **lower trunk/thigh/groin/buttocks**, and face (kids)
  - Vesiculopustules located at peripheral/expanding edge of plaques (helpful clue)
  - +/- mucosal involvement resembling MMP
  - Drug-induced LABD may have a TEN-like or morbilliform appearance → need biopsy and DIF
- Histopathology (cannot reliably distinguish from DH → need DIF):
  - **Early urticarial lesions**: **neutrophils diffusely lined up along BMZ** w/ basal vacuolar change (represents early epidermal separation) +/- neutrophilic papillitis
  - **Fully developed bullae**: subepidermal blister w/ neutrophils in blister cavity and in superficial dermis +/- neutrophilic papillitis
- DIF: **linear IgA** along BMZ
- IIF (+ in 65%): usually stains **epidermal side/roof** on salt-split skin
- Rx: **dapsone** (ToC) or sulfapyridine → rapid response (<72 hrs)
  - Oral steroids and immunosuppressants can be added in refractory cases (uncommon)
- Usually undergoes spontaneous remission within a few years

### Epidermolysis bullosa acquisita (EBA)

- Very rare, **acquired** subepidermal bullous disease
- Most commonly **adults**
- ↑incidence in East Asians and African Americans





**Figure 3-21.** Epidermolysis bullosa acquisita. (From James WD, Berger T, Elston D. et al. *Andrews' Diseases of the Skin: Clinical Dermatology*, 12th Ed. Elsevier. 2015)

- Associated diseases: **Crohn's disease/IBD (most common; 25%–50%)** > multiple myeloma, SLE, RA, diabetes, and thyroiditis
- Autoantigen: **IgG autoantibodies against NC1 domain of type VII collagen** (major component of **anchoring fibrils**, located in lamina densa/sublamina densa)
- MHC class II HLA-DR2 association
- Two distinct clinical patterns:
  - **Classic mechanobullous EBA** (Fig. 3-21): mimics a mild form of dystrophic EB; p/w **non-inflammatory bullae** (often hemorrhagic) and erosions on **acral/trauma-prone sites** (elbows, knees, and dorsal hands/feet) → may result in **"mitten" deformities** of the hands, syndactyly, and nail dystrophy/loss; bullous lesions **heal w/ atrophic scars, milia**, and dyspigmentation; scalp involved in 20% (→ scarring alopecia); Histopathology: **cell-poor subepidermal blister**
  - **Inflammatory (BP-like) EBA**: clinically **indistinguishable from BP**; p/w widespread vesicles and bullae affecting same sites as BP; lesions may heal **without classic scarring or milia** seen in mechanobullous form; may closely mimic MMP with erosions/vesicles in mouth, eyes, larynx, and esophagus → same complications; Histopathology: indistinguishable from BP → **must differentiate via DIF serration pattern, salt-split skin DIF, IIF, immunoblotting, or ELISA**
- DIF: perilesional skin shows a **broad linear band of IgG (> linear C3) (u-serrated pattern)** along BMZ
  - Pattern is opposite of BP (linear C3 > linear IgG; n-serrated pattern)
- IIF: circulating antibodies only detectable in 50%
- Salt-split skin: dermal (floor) staining
- Rx: **refractory to treatment**; may try systemic steroids, immunosuppressants, cyclophosphamide, colchicine, dapsone, IVIG, rituximab, or photopheresis

### Bullous systemic lupus erythematosus

- Rare autoimmune blistering disease seen in pts w/ **systemic lupus**
- Autoantigen: IgG autoantibodies against **collagen VII**

- Vesicles/bullae arising on urticarial background
- Histopathology: **neutrophil-predominant subepidermal blister**
- DIF: multiple immunoreactants (**IgG, C3, IgA, IgM**) **present in continuous granular pattern along BMZ**
- Salt-split skin: **dermal staining**
- Laboratory studies reveal serologic evidence of SLE (positive ANA and anti-DS DNA)
- Rx: **dapsone (ToC)**

### Dermatitis herpetiformis (Duhring's disease)

#### Epidemiology

- **Northern Europeans** most commonly affected; rare in blacks and Asians
- Average age of onset = **30–40 yo**, but kids and elderly may also be affected
- M > F
- Over 97% of DH and celiac disease (CD) patients have one or both of the following HLA II alleles:
  - **HLA-DQ2 (90%)**
  - **HLA-DQ8 (7%)**
  - **Boards note: older textbooks also cite HLA-B8, HLA-DR3, HLA-DR5, and HLA-DR7, but these are no longer felt to be directly associated**
- Strongly a/w other autoimmune diseases: **Hashimoto's thyroiditis** (most common; >50%) > **IDDM** > **pernicious anemia** > Addison's, alopecia areata, myasthenia gravis, vitiligo, and SLE

#### Pathogenesis

- **Gluten** is a grain protein found in **wheat, rye, and barley**
  - NOT in oats, rice, or corn
- **Gliadin** (antigenic component of gluten): soluble by-product of gluten
- **TTG2**: transglutaminase protein present in GI lamina propria; anti-TTG2 IgA antibodies responsible only for **gut involvement** (not skin) in DH and CD
- **TTG3** (epidermal transglutaminase): present in epidermis and dermal papillae; anti-TTG3 IgA antibodies responsible for **skin involvement** in DH
- Pathogenesis: ingestion of gluten-containing grains → gluten broken down into gliadin inside GI lumen → gliadin transported across GI mucosa to lamina propria → TTG2 in lamina propria deamidates gliadin → deamidated gliadin forms a covalent bond w/ TTG2 → **TTG2-gliadin complex is a neoantigen** recognized by HLA-DQ2 (or HLA-DQ8) on APCs → specific Th and B-cells activated → production of IgA autoantibodies against TTG2 or TTG2-gliadin complex → IgA antibodies bind to TTG2 complexes in lamina propria → neutrophil recruitment, damage to intestinal villi → enteropathy and villous atrophy → later, **epitope spreading** results in IgA autoantibodies against **epidermal transglutaminase (TTG3)** → circulating anti-TTG3 IgA binds locally to TTG3 **within dermal papillae** → neutrophils recruited to dermal papillae ("neutrophilic papillitis") → release elastase and MMPs → subepidermal blister most prominent above papillae

### Clinical features

- Extremely itchy **herpetiform vesicles** arising on urticarial plaques
  - Vesicles rupture easily → excoriations usually the only finding on exam
- Classic distribution (most helpful clue): **symmetric extensor extremities, buttocks, and back/neck** (> face/scalp)
  - Hemorrhagic palmoplantar lesions (useful clue)
- Only 20% of pts w/ DH have **symptomatic** GI disease, but >90% have some degree of gluten-sensitive enteropathy on GI biopsy

### Histopathology

- Ideally, biopsy an early blister for H&E: **subepidermal bulla** (most pronounced above dermal papillae), **neutrophilic papillitis** (neutrophils “stuffing” dermal papillae)
- In reality, findings often indistinguishable from LABD, but for test-taking purposes, DH has less confluent dermal neutrophilic inflammation and blisters are more localized to dermal papillae

### Laboratory testing

- DIF: **granular IgA deposits** +/- C3 in dermal papillae (90%)
  - Other pattern (10%): continuous granular IgA deposition along BMZ
  - Ideal biopsy site for DIF: 1 cm away from blister
- Serologic tests:
  - Antiendomysial** antibodies may be positive in DH (80%) and CD (>95%); titers correlate w/ degree of gluten-related enteropathy
  - Anti-gliadin antibodies may also be positive, but have high false (+) rates
- Check for G6PD deficiency before initiating dapsone

### Treatment

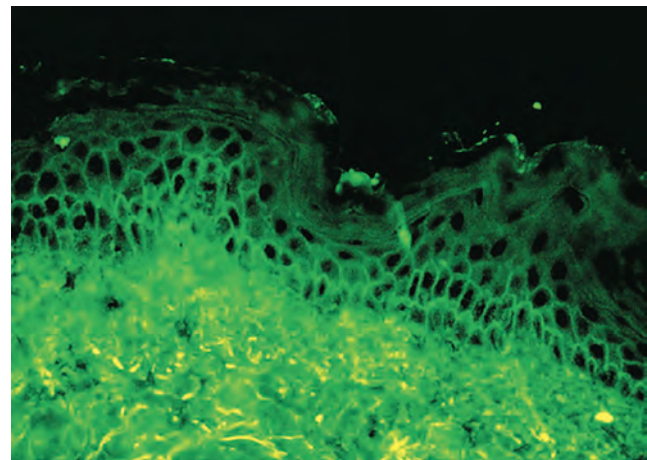
- Dapsone (ToC)**: controls skin disease very rapidly (<48–72 hrs); **no effect on GI disease/lymphoma risk**
  - If dapsone not tolerated, use sulfapyridine (good second line agent w/ ↓risk of hemolysis)
- Gluten-free diet**: controls both skin and GI disease; is only way to ↓risk of GI lymphoma (MALT-lymphoma)
- Avoid iodide** (ingestion or topically) since may → DH exacerbation

### Prognosis/clinical course

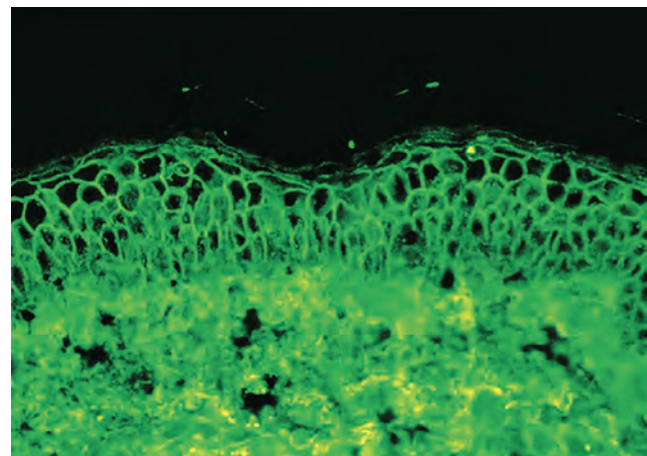
- Lifelong (90%), waxing and waning

## Comparative DIF images

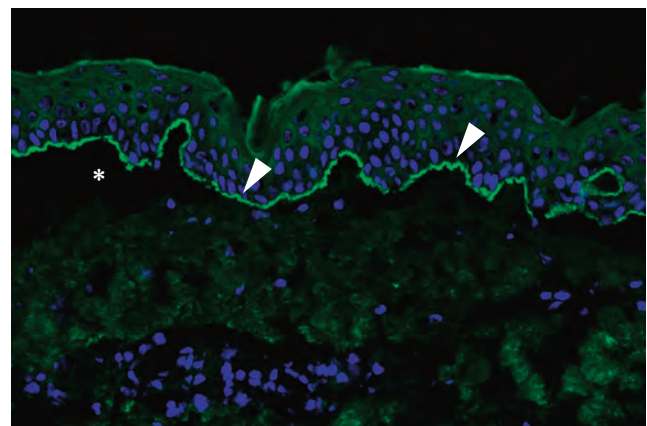
- PV (Fig. 3-22) – epidermis stained in chicken-wire pattern; strongest in lower epidermis (vs PF)
- PF (Fig. 3-23) – chicken wire pattern evident diffusely in epidermis (upper epidermis > lower epidermis)
- BP vs EBA (Fig. 3-24) and (Fig. 3-25)
- PNP – pemphigus erythematosus looks similar (Fig. 3-26)
- DH (Fig. 3-27) vs LABD (Fig. 3-28)
- PCT (Fig. 3-29)



**Figure 3-22.** Pemphigus vulgaris sera containing anti-desmoglein 3 (anti-Dsg3). IgG alone stains the cell surface in the lower epidermis. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

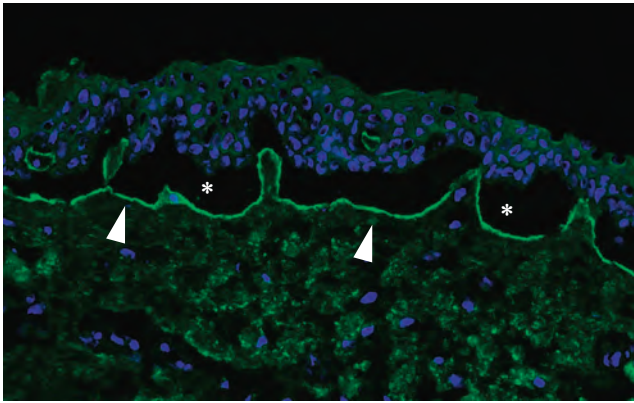


**Figure 3-23.** Pemphigus foliaceus sera, which contains only anti-Dsg1 IgG, stains the cell surfaces throughout the epidermis, but more intensely in the superficial layers. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

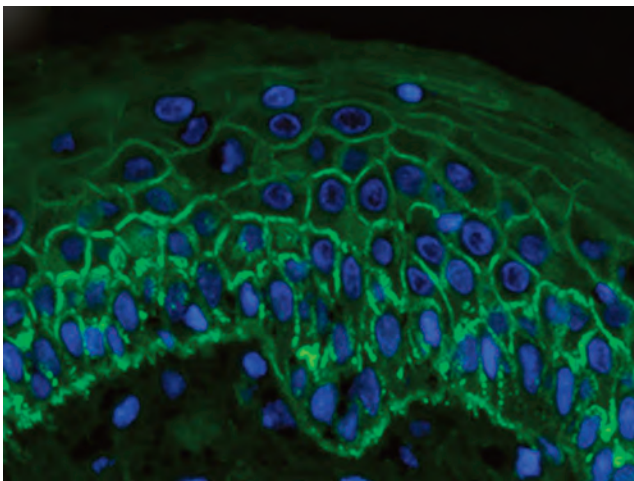


**Figure 3-24.** Circulating IgG autoantibodies from BP patients bind to the epidermal side (roof) of the salt-induced split (arrows); the artificial separation is indicated by an asterisk. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)





**Figure 3-25.** IgG autoantibodies from patients with EBA, anti-p200 pemphigoid, and certain forms of mucous membrane pemphigoid (e.g., with antibodies against laminin 5/332) react with the dermal side (floor) of the blister (arrows). Courtesy, H Pas, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



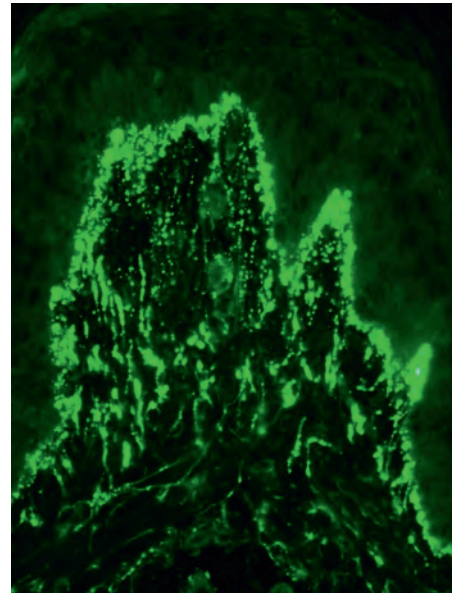
**Figure 3-26.** DIF of PNP patient skin sections shows IgG depositions along the epithelial cell surfaces of keratinocytes and often with concurrent basement membrane zone (BMZ) IgG depositions. (Poot AM, et al. Direct and indirect immunofluorescence staining patterns in the diagnosis of paraneoplastic pemphigus. *Br J Dermatol* 2016 Apr;174(4):912–915)

## Inherited blistering diseases

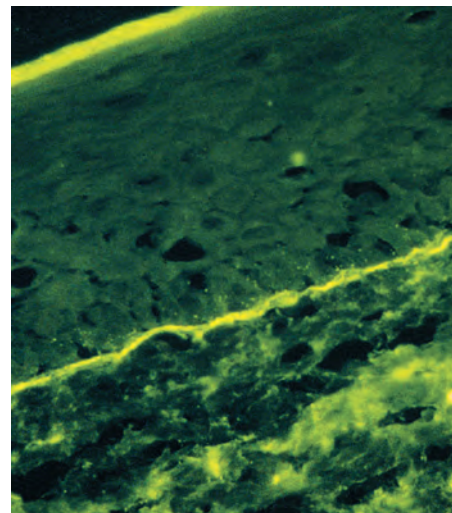
### Epidermolysis bullosa (see **Pediatric Dermatology** chapter)

#### Darier's disease (keratosis follicularis)

- AD; complete penetrance, variable expressivity
- Peak age of onset = **puberty** (70% prior to 20 yo)
- Chronic course, without spontaneous remission
- Mutation: ATP2A2 (encodes SERCA2 = calcium ATPase of endoplasmic reticulum) → defective  $\text{Ca}^{2+}$  sequestration into ER → impaired synthesis and folding of cell adhesion proteins → keratinocyte acantholysis and apoptosis
- Malodorous, warty, crusted, and red-brown papules/plaques in seborrheic distribution (Fig. 3-30); almost



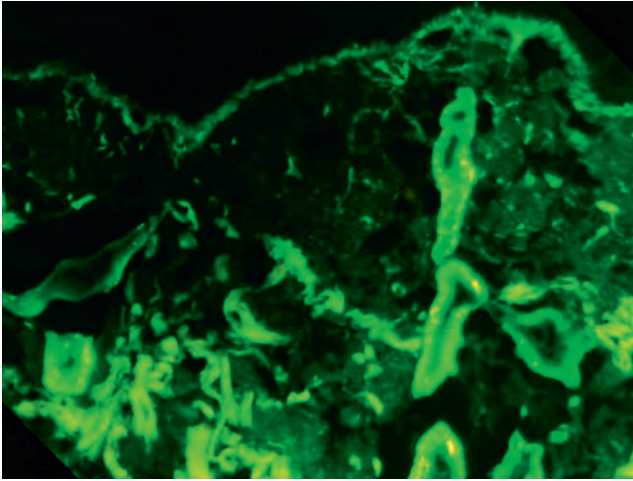
**Figure 3-27.** Dermatitis herpetiformis. Granular IgA deposition along the dermal-epidermal junction of normal-appearing skin adjacent to a lesion. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-28.** Linear IgA bullous dermatosis – direct immunofluorescence. A linear pattern of IgA deposition is present within perilesional skin. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

always see **keratotic palmar papules/pits**; **longitudinal red and white alternating nail streaks w/ distal “V-shaped” notching**; 50% have **oral cobblestoning** (hard palate most common)

- Segmental Darier's
  - **Type 1 (most common)**: Blaschkoid streaks of Darier's lesions; post-zygotic ATP2A2 mutation
  - **Type 2**: generalized Darier's w/ focal areas of severe involvement; heterozygous germline mutation + postzygotic loss of other allele



**Figure 3-29.** Homogeneous staining of C5b-9, accompanied by concomitant granular deposition within the microvasculature of this patient with underlying PCT. (Direct immunofluorescence; original magnification:  $\times 1000$ ). (From KE. Vasil, CM. Magro. *J Amer Acad Dermatol* 56(1):96–104. Elsevier. 2007)



**Figure 3-30.** Darier's disease. Typical seborrheic distribution of brown, keratotic papules. (Courtesy of Dr. Lawrence Lieblich).

- Prone to secondary infections (**Kaposi's varicelliform eruption** is most concerning)
- ↑incidence of **epilepsy**, intellectual impairment, **bipolar disorder**, and depression
- Histopathology: papillomatous epidermal hyperplasia w/ **epidermal acantholysis and dyskeratosis** (corps ronds and grains)
  - **Corps ronds**: large, **round**, acantholytic keratinocytes w/ dark nuclei surrounded by a bright pink rim of condensed keratin; located mostly in **spinous layer**



**Figure 3-31.** 47-year-old patient with axillary Hailey-Hailey disease (From M. Pretel-Irazabal, J.M. Lera-Imbuluzqueta and A. España-Alonso. *Dermatology (Actas Dermo-Sifiliográficas, English Edition)* 104(4):325–333. Elsevier. 2013.)

- **Corps grains**: **flattened** cells comprised of bright pink condensed keratin and a very thin dark nuclear remnant (looks like parakeratotic nucleus); located mostly in **s.corneum**
- Rx: **systemic retinoids** (>90% effective), topical steroids and retinoids, and topical antimicrobials to ↓odor

### Hailey-Hailey disease (familial benign chronic pemphigus)

- AD; complete penetrance, variable expressivity
- **Wider range of onset age than Darier's** (teens – 20 yo mostly, but may arise later)
- Mutation: **ATP2C1** (encodes hSPCA1, a  $\text{Ca}^{2+}$  ATPase of the Golgi apparatus) → defective  $\text{Ca}^{2+}$  sequestration into golgi → impaired processing of proteins involved in cell-cell adhesion → acantholysis
- Most commonly affects **intertriginous sites** (lateral neck, inframammary, **axillae**, **groin**, and perianal)
- Subtle, flaccid vesicle on normal or inflamed skin → ruptures to give **macerated, eroded plaques** (**Fig. 3-31**), often w/ circinate shape
- **No mucosal involvement** (helps DDx from Darier's)
- Prone to secondary infections (**Kaposi's varicelliform eruption** is most concerning)
- Histopathology: **psoriasiform hyperplasia** (differentiates from pemphigus) w/ **diffuse acantholysis** (resembling a "dilapidated brick wall"); fewer dyskeratotic keratinocytes than Darier's
- Rx: topical steroids; **surgical intervention** (e.g., CO<sub>2</sub> laser ablation) is very effective
  - Retinoids not nearly as effective as in Darier's

### Other blistering diseases

- Multiple non-immunobullous and non-inherited diseases may cause blistering disorders
- Clinicopathologic correlation is often needed for accurate diagnosis
- See [Table 3-9](#) and [Table 3-10](#)

**Table 3-9.** Other Blistering Disorders

Disease	Clinical Setting	Clinical Presentation	Blister Location
Bullous diabeticorum	Longstanding diabetics w/ peripheral neuropathy, retinopathy, or nephropathy	p/w sudden eruption of <b>tense, non-inflammatory</b> , clear fluid-filled vesicles/ bullae, 0.5 to several cm, on <b>feet</b> (>lower legs > hands > forearms); histopathology: <b>cell-poor subepidermal blister</b> ; DIF negative; Rx: spontaneous resolution in 2–6 wks; may aspirate if uncomfortable	Subepidermal
Coma blister	Coma due to meds ( <b>barbiturates</b> > <b>benzos</b> , alcohol, opioids), or non-drug-induced coma	<b>Tense blisters</b> arising on <b>sites of pressure</b> 48–72 hrs after loss of consciousness; blisters due to pressure-induced necrosis; histopathology: cell-poor subepidermal blister w/ <b>sweat gland necrosis</b> +/- epidermal necrosis; DIF negative; Rx: heals spontaneously in 1–2 wks	Subepidermal
Friction blisters	New pair of <b>ill-fitting shoes</b> ; sports or military involvement	Very common in <b>young, physically active</b> , repetitive friction; initially red macules at site of friction → painful <b>intraepidermal blisters</b> w/ blood-tinged fluid; histopathology: pauci-inflammatory <b>blister just under granular layer</b> ; DIF negative; Rx: heals spontaneously; may aspirate to relieve pressure	Intraepidermal
Bullous small vessel vasculitis	Pts w/ small vessel vasculitis (cutaneous or systemic)	LCV w/ superimposed hemorrhagic vesicles and bullae, usually on <b>distal extremities</b> → may ulcerate; histopathology: <b>LCV w/ massive subepidermal edema/bullae</b> and epidermal necrosis	Subepidermal
Bullous drug eruptions	Pts receiving meds	See Table 3-10	See Table 3-10
Bullous Arthropod Assault	Most common in children or pts with <b>hematologic malignancy (CLL &gt; mantle cell lymphoma, NK/T-cell lymphoma)</b>	<b>Grouped pruritic papules</b> w/ central blistering; may have persistent papulonodules (persistent arthropod assault); <b>pts w/ lymphoma may have reaction in absence of definitive insect bite (“bug bite-like reactions”)</b> ; histopathology: eosinophilic spongiosis, <b>superficial and deep PV/PA lympho-eosinophilic inflammation</b> (+/- flame figures), superficial dermal edema; Rx: topical steroids, oral antihistamines	<b>Intraepidermal</b> > subepidermal blister (may occur if dermal edema severe)
Delayed postburn/postgraft blisters	Blisters at sites of prior trauma (burns, graft site)	Tense vesicles/bullae appearing weeks to months (avg 37 days) after original wound has completely healed; <b>due to fragility of new DEJ</b> ; histopathology: cell-poor subepidermal blister; negative DIF; Rx: spontaneous resolution	Subepidermal
Edema blisters	Anasarca or acute exacerbation of chronic edema	<b>Tense blisters</b> in edematous dependent sites ( <b>distal LE, feet</b> most common); histopathology: cell-poor subepidermal bullae with massive dermal edema and epidermal spongiosis; Rx: treat underlying edema, compression wraps	Subepidermal

(Modified from Table 33.1 in Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012).

**Table 3-10.** Bullous Drug Eruptions

Disease	Characteristic Features	Commonly Implicated Drugs
Fixed drug eruption	Sharply circumscribed <b>erythematous to dusky</b> violaceous patches Central blisters or erosions may appear Often resolves with <b>postinflammatory hyperpigmentation</b> Recurrence at same location(s) following drug re-exposure	<b>Sulfonamides, NSAIDs, tetracyclines</b> , barbiturates, aspirin, acetaminophen (paracetamol), metronidazole, phenolphthalein
Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	Prodrome of fever and <b>painful skin</b> Areas of dusky erythema associated with epidermal detachment (varying from <10% [SJS] to >30% [TEN]) Mucosal involvement	NSAIDs, antibiotics (sulfonamides and $\beta$ -lactams), anticonvulsants, allopurinol
Drug-induced autoimmune blistering diseases	Primarily linear IgA bullous dermatosis, pemphigus, bullous pemphigoid Diagnosis based on histologic findings, immunofluorescence studies, and drug history	<u>Linear IgA bullous dermatosis</u> : <b>vancomycin</b> > $\beta$ -lactams, captopril, NSAIDs <u>Pemphigus</u> : <b>penicillamine, captopril</b> , $\beta$ -lactams, gold <u>Bullous pemphigoid</u> : diuretics (especially <b>furosemide</b> ), antibiotics
Drug-induced pseudoporphyria	Eruption resembles porphyria cutanea tarda Porphyrin determinations are within normal limits	NSAIDs (especially <b>naproxen</b> ), nalidixic acid, thiazides, furosemide, tetracyclines
Acute generalized exanthematous pustulosis	Acute onset, usually occurring within 2 days of drug exposure Areas of erythema studded with pustules; occasionally vesicles Fever, malaise, leukocytosis	<b><math>\beta</math>-lactams</b> , macrolides, pristinamycin, terbinafine, calcium channel blockers (diltiazem), hydroxychloroquine, carbamazepine, acetaminophen, metronidazole
Phototoxic drug eruptions	Limited to sun-exposed areas Resembles exaggerated sunburn	<b>Tetracyclines</b> (especially doxycycline), <b>quinolones, psoralens</b> , NSAIDs, diuretics
Bromoderma and iododerma	<b>Acneiform lesions</b> , papulopustules, nodules, or even <b>vegetating lesions</b> simulating pemphigus vegetans Clear or hemorrhagic blisters can develop (more common in iododerma)	Bromides, iodine-containing drugs (e.g. amiodarone), radiographic contrast media
Palmoplantar erythrodysesthesia (acral variant of toxic erythema of chemotherapy)	Painful erythema develops primarily on the palms, soles and digits following chemotherapy administration The skin becomes edematous, its color changes to dark red or violet, and blisters and erosions may develop	<b>Cytarabine</b> , doxorubicin, capecitabine, 5-fluorouracil (especially prolonged infusions), multi-kinase inhibitors (e.g., sorafenib, sunitinib), busulfan, taxanes, clofarabine, pralatrexate

(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

Occasionally, eczematous drug reactions (e.g., secondary to warfarin, calcium channel blockers) and systemic contact dermatitis can be papulovesicular; patients with drug reaction eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) can also develop vesicles.

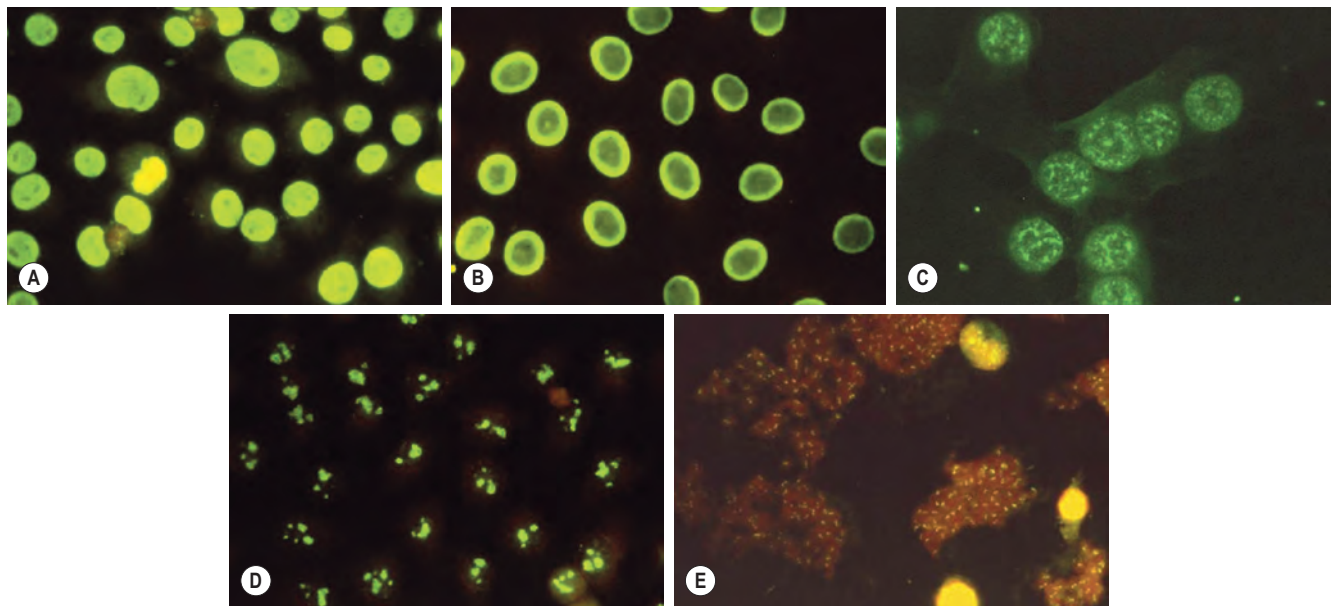


### 3.5 CONNECTIVE TISSUE DISEASES (CTDs) AND SCLEROSING DERMOPATHIES

#### Connective tissue disease laboratory studies

##### Antinuclear antibodies (ANA)

- ANAs are autoantibodies that target various nuclear antigens:
  - Extractable nuclear antigens (ENAs):
    - Ro/SSA: most strongly a/w Sjogren syndrome (70%) and neonatal lupus (~100%), but also present in SCLE (75%–90%) and SLE (50%)
    - La/SSB: most strongly a/w Sjogren syndrome (40%), but also in SCLE
    - Scl-70 (DNA topoisomerase I): most strongly a/w diffuse SSc (60%)
    - Jo-1 (histidyl tRNA synthetase): DM/PM with antisynthetase syndrome
    - Smith (Sm): highly specific for SLE (only 10%–30% sensitive)
    - RNP (U1 RNP): very high titers correlate with MCTD (100%); lower titers in SLE
  - Non-ENA targets:
    - dsDNA (double-stranded DNA): highly specific for SLE (60% sensitive), a/w lupus nephritis, correlates with lupus band test from sun-protected skin
    - Histone: most a/w drug-induced SLE (95%)
    - Centromere: a/w CREST (80%)
- ANAs may be detected by ELISA (newer, cheaper method) or IIF (older but more sensitive method; substrate is Hep2 cancer cell line)
  - Despite its limitations, the classic IIF ANA test still remains the most efficient screening test for systemic autoimmune connective tissue disorders
  - ELISA studies useful for identifying specific antigenic targets → helpful in serologically narrowing the diagnosis between CTDs
- ANA titer = highest dilution of patient's serum that still produces fluorescence (considered **positive** if >1:40)
- Range of ANAs in "healthy" individuals
  - ≥1:40 (20%–30%)
  - ≥1:80 (10%–12%)
  - ≥1:160 (5%)
  - ≥1:320 (3%)
- Rates of ANA positivity:
  - SLE: 99%
    - Less than 1% of SLE patients have negative ANA by IIF → highly unlikely to get false (–) result by current testing methods!
  - SSc: 90%
  - SjS: 70%
  - DM/PM: 40%–65%
- Common ANA IIF patterns (and corresponding antigenic targets by ELISA) (Fig. 3-32):
  - Homogenous (aka "diffuse"): anti-dsDNA and anti-histone antibodies
    - a/w SLE and drug-induced SLE
  - Peripheral (aka "rim"): dsDNA
    - a/w SLE
  - Speckled (aka "particulate"): Ro/SS-A, La/SS-B, U1RNP, Smith, RNA polymerases, and Scl-70
    - Non-specific but may be a/w Sjogren's and MCTD



**Figure 3-32.** Detection of antinuclear antibodies (ANA) by indirect immunofluorescence. Utilizing HEp-2 tumor cells as the substrate. Patterns of nuclear immunofluorescence include: homogeneous (A); peripheral (B); speckled (C); nucleolar (D); and centromeric (E). Part (E) is illustrated on a chromosome preparation during metaphase arrest. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Nucleolar: RNA processing molecules (fibrillar/anti-PM/Scl)
  - a/w SSc, polymyositis-SSc overlap
- Centromere (aka “discrete speckled”): anti-centromere antibodies
  - Specific for CREST
- Know the autoantibody associations for each AI-CTD (highly testable!) (Table 3-11)

### Lupus band test (LBT)

- Granular continuous band of immunoglobulin deposits (IgM > IgG > IgA) and complement (C3) at DEJ in lesioned and non-lesioned skin of sun-exposed or sun-protected sites in **patients w/ SLE** visualized via DIF
- Three different types of LBTs exist:
  - **Lesional LBT**
    - High sensitivity in patients w/ SLE
    - LBT may also be positive in patients with CCLE (60%–80%)
    - Helpful in differentiating from other rashes in non-SLE patients
      - ◆ Can see false (+)s in rosacea, telangiectasias and PMLE → band is usually weaker in intensity and more focal/interrupted
    - Positive LBT seen in <5% of dermatomyositis
    - ↑# of immunoreactants → ↑specificity for SLE
  - **Sun-exposed, non-lesional skin** (shoulder, proximal extensor forearm)
    - Positive in 70%–80% of SLE
    - Useful in making diagnosis of SLE in patients without skin lesions
    - 25% of people without SLE will demonstrate a weak interrupted linear and granular DEJ deposition of IgM and C3 (less frequently IgG, IgA, and C3), which usually does not meet criteria for a positive LBT
  - Sun-protected, non-lesional skin (medial flexor forearm, medial upper arm, and buttocks)
    - Positive in 35%–55% of SLE
    - Useful for measuring disease activity and assessing prognosis
    - **Correlates with anti-dsDNA autoantibodies** → a/w severe extracutaneous disease including renal disease

### Lupus erythematosus

- There are **three major forms of cutaneous lupus**: acute (ACLE), subacute (SCLE), and chronic (CCLE)
  - These three forms are not mutually exclusive → pts may have more than one cutaneous morphology at any given time
  - **Every form of cutaneous lupus may be seen in the setting of SLE or as an isolated cutaneous disease**
  - The degree of association with SLE varies by cutaneous subtype (Table 3-12)
- **All patients with cutaneous lupus should be evaluated for systemic disease (SLE)** via clinical exam, biopsy (H&E and DIF), and serologic studies

### Chronic cutaneous lupus erythematosus (CCLE)

#### Epidemiology

- Female predominance
- **Discoid lupus (DLE) accounts for the majority of CCLE cases**
  - 40%–70% of SLE patients will have discoid lesions
  - However, only 5%–20% of patients with DLE progress to SLE
    - 5% for patients w/ head-only involvement
    - 20% for patients w/ diffuse involvement
  - **African Americans** more commonly affected w/ DLE

#### Pathogenesis

- UVR (UVB > UVA) is important trigger for all CCLE subtypes
- Type I interferon signature w/ CD4+ T-helper 1 (Th1) cells and CD8+ cytotoxic T-cell recruitment and activation
- Tobacco:
  - Smoking is a risk factor for DLE
  - Stopping may help resolve recalcitrant lesions
- Genetic predisposition (multiple genes)

#### CCLE clinical subtypes

1. Discoid lupus erythematosus (DLE)
  - Begin w/ red macules or plaques → later develop scale, atrophy, and scarring, w/ **central hypopigmentation and peripheral hyperpigmentation** (more apparent in darker-skinned patients) (Fig. 3-33)
  - Languette du chat (cat’s tongue): carpet “tack-like” spines on undersurface of scale
  - Typical locations: **face, scalp** (cicatricial alopecia), and ears (esp. **conchal bowl**)
    - Can also occur in photoprotected sites
    - 25% have mucosal involvement
  - ANA (+) in 5%–25%
  - DLE variants:
    - Localized DLE
      - Above neck only
    - Widespread DLE
      - Above and below neck
      - **Stronger association w/ SLE**, more likely to have serologic abnormalities
    - Childhood DLE
      - Higher rate of progression to SLE
2. Hypertrophic (verrucous) LE
  - Thick, hyperkeratotic and verrucous scaling plaques w/ indurated border
  - ↑risk SCC (akin to hypertrophic LP)
  - Typical locations: extensor forearms, face, and upper trunk (sun-exposed sites)
    - Favors **upper half of body** (vs hypertrophic LP = lower half)
  - Usually accompany typical discoid lesions
3. Chilblain lupus erythematosus
  - Red or dusky purple papules/plaques on **fingertips, rims of ears, calves, and heels**



Table 3-11. High-Yield Autoantibodies in Connective Tissue Diseases			
Target	Prevalence (%)	Molecular Specificity	Key Association
<b>Lupus Erythematosus (listed prevalence is for SLE)</b>			
ANA	99	N/A	Most sensitive serologic test for SLE → most common IIF pattern in SLE = <b>homogenous, peripheral</b> <b>SCLE positive in 60%–80%</b> (speckled/particulate IIF) <b>DLE positive in 5%–25%</b>
ssDNA	70	Denatured DNA	<b>Risk for developing SLE in DLE patients</b> ; also seen in linear morphea
C1q	60	C1q component of complement	Severe SLE, <b>hypocomplementemic urticarial vasculitis syndrome</b>
dsDNA	60	Double-stranded (native) DNA	<b>Highly specific test for SLE</b> ; a/w <b>LE nephritis</b> → useful for monitoring nephritis activity
U1RNP	50 ( <b>low titers</b> )	Spliceosome RNP	Overlapping features with other AI-CTDs; high titers in MCTD (100%)
Ro/SSA	50	hyRNP	<b>Neonatal LE/congenital heart block (99%)</b> ; <b>SCLE</b> (75%–90%); primary SjS (70%); a/w photosensitivity
Cardiolipin	50	Cardiolipin (phospholipid)	<b>Antiphospholipid syndrome in SLE</b> : recurrent abortions, thrombocytopenia, hypercoagulable state, livedo reticularis, leg ulcers, acral infarction, hemorrhagic cutaneous necrosis
Histone	40	Histones	<b>Drug-induced SLE</b>
Smith (Sm)	10–30	Spliceosome RNP	<b>Highly specific for SLE</b> ; higher prevalence in African Americans and Asians (30%–40%)
β2 glycoprotein	25	Cofactor for cardiolipin	High risk of thrombosis in SLE; primary antiphospholipid syndrome
rRNP	7–15 (40% in Asians)	Ribosomal P proteins	Highly specific for SLE; a/w <b>neuropsychiatric LE</b>
Ku	10	DNA repair complex	Overlap syndromes with DM/PM and SS
<b>DM/PM</b>			
ANA	40	N/A	Most common IIF patterns: <b>speckled, nucleolar</b>
p155/140	80 (amyopathic) 10–30 (classic)	Transcriptional intermediary factor 1-γ	<b>Clinically amyopathic DM</b> ; <b>cancer-associated DM</b> (adults); severe cutaneous disease in adults and kids
p140	25 (Juvenile DM)	NXP-2	<b>Juvenile DM with calcinosis</b>
Aminoacyl tRNA synthetases	Up to 20	tRNA synthetases	<b>Anti-synthetase syndrome</b> : myositis, <b>mechanic's hands</b> , arthritis, Raynaud's phenomenon, <b>severe ILD</b>
<b>Anti-Jo1</b>	Jo1 (20)		
<b>Anti-PL7</b>	PL7 (5)		
<b>Anti-PL12</b>	PL12 (3)		
<b>EJ/OJ</b>	EJ/OJ (<1)		
Mi-2	15	<b>Helicase</b>	<b>Classic DM skin findings</b> , mild muscle disease; <b>good response</b> to treatment
MDA5/ CADM-140	10–15	MDA5	<b>CADM w/rapidly progressive ILD</b> (adults and kids); distinctive skin findings (skin/oral ulcers, palmar papules, mechanic's hands, panniculitis)
SRP	5	Signal recognition particle	Fulminant DM/PM with <b>cardiac involvement, poor prognosis</b>
Ku	3	DNA repair complex	DM overlap syndromes with SLE, Sjogren's, or SS
SAE	N/A	Post-translational modification	Some cases of adult CADM
<b>Systemic Sclerosis</b>			
ANA	95	N/A	Most common patterns: speckled, nucleolar, <b>centromere (CREST)</b>
Centromere	30 (PSSc) 80 (CREST)	CENP-B	Most specific for <b>CREST</b> , a/w pulmonary HTN
Scl-70	60 (PSSc) 15 (CREST)	DNA topoisomerase I	Most strongly a/w <b>PSSc</b> with pulmonary fibrosis
<b>RNA polymerases (I and III)</b>	45 (PSSc) 6 (CREST)	RNA polymerase I / III	High levels correlate w/ <b>severe skin involvement</b> and <b>renal crisis</b> in PSSc
Fibrillarin (U3RNP)	5 (overall)	U3RNP	a/w internal organ involvement
<b>Morphea</b>			
ANA	40	NA	N/A
Topoisomerase IIα	75	Topo IIα	Not used clinically
ssDNA	50	NA	Most prevalent in <b>linear morphea</b> , correlates w/ disease severity/activity
Histones	35	Histones	Most prevalent in <b>linear and generalized morphea</b> , correlates w/ disease severity/activity
Fibrillin-1	30	Fibrillin-1 (component of ECM)	Rarely positive in PSSc or CREST

**Table 3-11.** High-Yield Autoantibodies in Connective Tissue Diseases—cont'd

Target	Prevalence (%)	Molecular Specificity	Key Association
<b>Rheumatoid Arthritis</b>			
Rheumatoid factor	80	Fc portion of IgG	<u>Low levels:</u> very nonspecific, may be seen in other AI-CTDs, infections, liver dz, sarcoid, systemic vasculitides <u>High levels:</u> a/w <b>severe, crippling, erosive RA</b> and extra-articular manifestations of RA (systemic vasculitis, neuropathy); may also have high levels in <b>mixed cryoglobulinemia</b> (types II and III) secondary to Hep C infection
Cyclic citrullinated proteins	70	CCP proteins in skin (filaggrin) and joints	a/w <b>severe RA</b> ; also a predictor for development of RA
<b>Sjogren's Syndrome</b>			
$\alpha$ -fodrin	70	Actin-binding protein (involved in secretion)	<b>Most specific</b> antibody for SjS
Ro/SSA	60-70	hyRNP	Also important in neonatal LE (~99%) and SCLE (may be a/w photosensitivity)
La/SSB	20-40	hyRNP	N/A
<b>Mixed Connective Tissue Disease (MCTD)</b>			
U1RNP	100 (by definition)	Spliceosome RNP	Low titer positivity can be seen in SLE

(Modified from Tables 40.2–40.5 in Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 3-12.** Different Forms of Cutaneous Lupus and Their Association With Systemic Lupus Erythematosus (SLE)

Type of Cutaneous Lupus	Association with SLE
• Acute cutaneous lupus erythematosus (ACLE)	++++
• Subacute cutaneous lupus erythematosus (SCLE)	++
• Chronic cutaneous lupus erythematosus (CCLE)	
Localized DLE (head and neck)	+
Widespread/disseminated DLE	++
Hypertrophic DLE	+
Lupus erythematosus tumidus (LET)	+/-
Lupus panniculitis	+
Chilblain lupus	++
• Other variants	
Bullous eruption of SLE	++++
Rowell's syndrome	++ to ++++

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Chronic relapsing course
  - Precipitated by cold, but often **persist year-round** (vs non-lupus-associated chilblains)
4. **Tumid lupus erythematosus**
- Edematous, indurated, erythematous, often **annular** plaques without epidermal involvement (Fig. 3-34)
    - Plaques may have central clearing
  - Typical locations: **face and trunk**
  - Responds well to antimalarials
  - Considered to be on a clinical spectrum w/ Jessner's and reticular erythematous mucinosis (REM), with similar findings on histology
  - Differentiating Tumid LE vs Jessner's vs REM:
    - Jessner's: similar clinical appearance, but has CD8+ predominant infiltrate w/ ↓mucin
    - REM is histologically identical to tumid LE, but is morphologically distinctive (erythematous macules

**Figure 3-33.** Extensive scarring from discoid lupus erythematosus. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

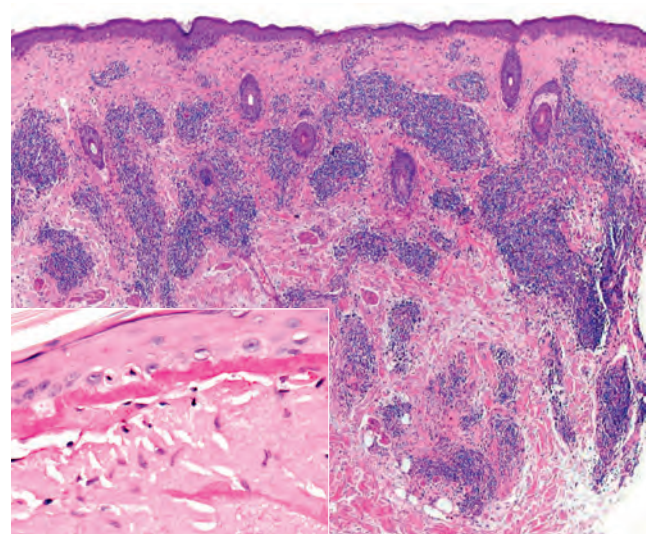
and papules or plaques on mid back/chest in a reticular pattern)

5. **Lupus erythematosus panniculitis/profundus**

- Indurated, non-tender, subcutaneous nodules or plaques that **heal w/ atrophy**
- Overlying skin often normal, but may have **overlying discoid changes**
- Typical locations: face, **upper arms, upper trunk, breasts, buttocks, and thighs**



**Figure 3-34.** Lupus erythematosus tumidus. Annular pink plaques on the chest. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-35.** Histologic features of cutaneous lupus erythematosus (LE). Chronic discoid LE showing focal interface dermatitis and dense perivascular and periadnexal lymphoid infiltrates throughout the entire dermis. A thickened basement membrane is a characteristic finding and can be highlighted by PAS staining (insert). Courtesy, Lorenzo Cerroni, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Antimalarials effective
- 15% a/w SLE (panniculitis may be first sign)
- 6. **Discoid lupus-lichen planus overlap**
  - Coexisting DLE and lichen planus w/ overlap lesions
  - Palmoplantar involvement is characteristic
  - DDx: a lichen planus-like rash can also occur in SLE patients on antimalarials
- 7. **Mucosal LE**
  - Does not include non-lupus specific mucosal ulcers a/w SLE
  - Most commonly seen in conjunction w/ cutaneous DLE
  - Lesions:
    - Classic plaque with central erythema and surrounding white keratotic border, usually on hard palate
    - Discoid lesions most commonly on the lip
  - Typical locations: buccal mucosa, hard palate, and vermillion lip (lower > upper)
  - ↑risk SCC
  - Presence of ulceration → a/w ↑risk for systemic involvement

#### Laboratory testing

- (+/-)ANA, leukopenia, and ↑ESR
  - Serologic abnormalities more common in patients w/ widespread DLE

#### Histopathology

- Discoid lupus
  - H&E: compact orthohyperkeratosis, **vacuolar interface dermatitis** w/ necrotic keratinocytes and pigment incontinence, **epidermal atrophy**, **BMZ thickening**, **follicular plugging**, superficial and **deep** perivascular/periadnexal lymphohistiocytic inflammation with plasma cells, and **mucin deposition** (Fig. 3-35)
    - Lacks eosinophils
  - DIF
    - LBT(+) on lesional skin in 75%; ideal to choose lesion that has been present for a few months or more
      - ◆ More likely to be positive on head/neck and extremities compared with trunk

- Hypertrophic (verrucous) LE
  - Similar histologic features as DLE but w/ greater orthohyperkeratosis and **endophytic buds of hyperplastic follicular epithelium** (> interfollicular epidermal hyperplasia)
    - Pseudoepitheliomatous hyperplasia is **often mistaken for SCC**
- Chilblain LE
  - Demonstrates features of both chilblains (papillary edema, perivascular and dermal lymphohistiocytic infiltration) and DLE
  - DIF: (+) LBT
- Tumid LE
  - No significant epidermal changes (e.g., lacks follicular plugging, vacuolar interface, and BMZ thickening)
  - Shares characteristic dermal features of DLE:
    - PV/PA lymphoid aggregates in upper and lower dermis
    - **Massive mucin deposition** (more than classic DLE; amount rivals that seen in DM)
  - Histologically similar to REM and Jessner's, except Jessner's has CD8+ predominant infiltrate and lacks mucin
  - DIF: (+) LBT in 50%
- LE panniculitis
  - May have histologic findings of overlying DLE without clinical findings of DLE
  - Dermal mucin deposition
  - Subcutaneous findings:
    - Lymphocytic **lobular panniculitis**
    - Hyaline ("waxy pink") fat necrosis
    - Nodular lymphoid aggregates

- Fat lobules may be rimmed by lymphocytes
  - ◆ **Important to differentiate from subcutaneous T-cell lymphoma** (atypical cells, lacks dermal lymphoid nodules, lacks mucin)
- DIF: (+) LBT in 35%–70%
- Discoid lupus-lichen planus overlap
  - Typical lesions of LE or LP will demonstrate H&E and DIF findings for that condition
  - Overlap lesions may show features typical for both
- Mucosal LE
  - Hyperkeratosis, atrophy of rete pegs, vacuolar-to-lichenoid interface dermatitis; superficial and deep perivascular lymphocytic infiltrate
  - DIF: (+) LBT

### Treatment

- Treatment algorithm: (Fig. 3-36)

### Prognosis/clinical course

- 5%–20% progress to SLE
- ↑risk of progression w/ widespread DLE and childhood DLE

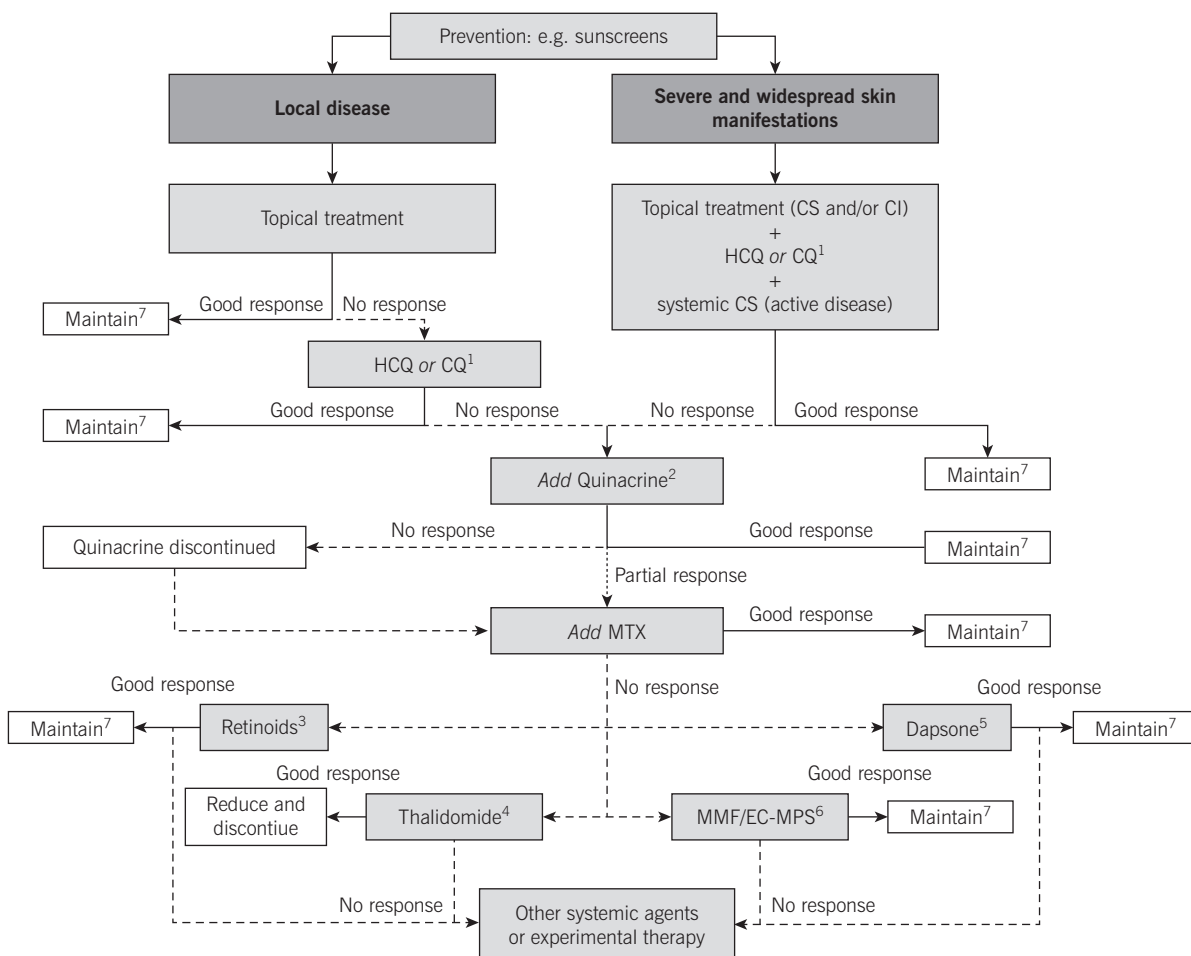
## Subacute cutaneous lupus erythematosus (SCLE)

### Epidemiology

- Female predominance (4:1)
- More common in whites (vs DLE)
- 30%–50% of patients w/ SCLE lesions will eventually meet criteria for SLE, but most usually only have mild disease

### Pathogenesis

- Proposed mechanism: UVR-induced apoptosis → apoptotic bodies containing high levels of nuclear antigens (e.g., Ro, La, DNA) + reduced clearance of apoptotic cells (particularly in complement-deficiency related LE) → loss of immune tolerance → release of proinflammatory cytokines and production of ANAs, most importantly anti-Ro/SS-A autoantibodies
- Genetic associations:
  - HLA-B8 (strongest association), HLA-DR3, and others
  - Hereditary complement deficiencies



**Figure 3-36.** Cutaneous lupus erythematosus: update of therapeutic options. Algorithm of treatment for CLE. Topical agents include topical steroids, calcineurin inhibitors, and retinoids. Consider retinoids earlier for discoid lupus-lichen planus overlap. HCQ, hydroxychloroquine; CQ, chloroquine; MTX, methotrexate; MMF, mycophenolate mofetil; EC-MPS, mycophenolate sodium. (From Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: Update of therapeutic options Part I. J Amer Acad Dermatol 2011;65:e179–e193)



- Antibodies
  - **Anti-Ro/SS-A** (75%–90%)
    - Thought to be pathogenic in SCLE
    - May cause clinical overlap w/ Sjogren's
- Complement
  - SCLE is a/w **complement deficiencies**, especially deficiencies in the **early intrinsic pathway** (C1q/r/s, C2, and C4)

#### Clinical features

- Often has a chronic, relapsing course
- **Photosensitivity** prominent in 50%
- Two clinical variants:
  - **Papulosquamous SCLE**: psoriasiform plaques (Fig. 3-37)
  - **Annular SCLE**: scaly polycyclic annular plaques with central clearing
- Typical locations: sun-exposed areas of **lateral face (central face spared)**, neck, V-chest, and **upper back/** extremities
- Often heals w/ hypopigmentation, but no scarring
- May have clinical overlap w/ Sjogren's (both have Ro/SS-A autoantibodies)
- Systemic manifestations are common, but **only 30%–50% fully meet criteria for SLE**
  - **Arthritis/arthralgias** = most common systemic finding (up to 70%)

#### Laboratory testing

- Antibodies
  - **Anti-Ro/SS-A** (75%–90%)
  - **Anti-La** (30%–40%)
  - **ANA** (60%–80%; usually in a speckled/particulate pattern)
- Other
  - Leukopenia (20%)



**Figure 3-37.** Subacute cutaneous lupus erythematosus (SCLE), papulosquamous. Psoriasiform lesions coalesce to form retiform arrays. Courtesy of Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. *Best Pract Res Clin Rheumatol* 2013;27(3):391–404

#### Histopathology

- Compact hyperkeratosis, prominent **epidermal atrophy**, **vacuolar interface** dermatitis w/ pigment incontinence, BMZ thickening, PV/PA lymphoid aggregates (limited to superficial dermis) w/ scattered plasma cells, and **mucin** deposition
  - Lacks eosinophils and follicular plugging
- DIF:
  - (+) LBT in 60%–85% (usually not as thick or intensely stained as in DLE)

#### Treatments

- First line: **antimalarials and sun protection**
- Recalcitrant: may require other immunosuppressive meds (see Fig. 3-34)

#### Additional boards factoids

- Always think about drugs and complement deficiencies!
- **Drug-induced SCLE**:
  - **Skin always involved!**
  - **Rare to have systemic involvement**
  - **Photosensitive** papulosquamous eruption (often psoriasiform to lichenoid) w/ annular plaques on upper body and extensor upper extremities
  - Antibodies: **anti-Ro/SS-A (80%)**, anti-La/SS-B
  - Most important implicated drugs: **HCTZ (most common)**, **terbinafine**, **griseofulvin**, NSAIDs (piroxicam), CCBs, antihistamines, PPIs, docetaxel, ACE inhibitors, and TNF- $\alpha$  inhibitors (most commonly etanercept)

### SCLE-like syndromes

#### Neonatal lupus erythematosus (NLE)

- Epidemiology
  - **Female predominance** for NLE of skin (3:1) and cardiac NLE (2:1)
- Pathogenesis
  - Result of transplacental passage of maternal autoantibodies, most importantly **anti-Ro/SS-A (99%)**
    - Autoantibodies can result in heart block requiring pacemaker
    - Unselected women with anti-Ro/SS-A antibodies  $\rightarrow$  1%–2% risk of having child with NLE
    - Women w/ SLE or another defined CTD with anti-Ro/SS-A antibodies  $\rightarrow$  15% risk having a child w/ NLE
    - Women who have a **prior child w/ NLE**  $\rightarrow$  **25% risk of NLE in subsequent children**
- Clinical features
  - Cutaneous findings:
    - Lesions arise within first weeks of life but usually not present at birth
    - Skin lesions (similar to adults w/ SCLE but more prominent facial involvement):
      - ◆ Photosensitivity
      - ◆ Periorbital erythema = “**raccoon eyes**”

- ◆ **Annular, polycyclic erythematous plaques** w/ central clearing and raised red border, fine scale, typically located on scalp, neck, or face
- ◆ Non-scarring
- ◆ **Resolves w/ dyspigmentation and telangiectasias**
- Systemic findings:
  - Cardiac (70% overall have some cardiac abnormality; 30%–40% have congenital third degree heart block)
    - ◆ Heart block is **almost always present by birth**, developing in utero between 16 and 24 weeks gestation
    - ◆ Usually p/w **bradycardia and irreversible complete heart block (third degree)**
      - ➔ Occasionally p/w first or second degree heart block → may progress to complete heart block
  - Hepatobiliary disease (50%)
    - ◆ p/w transient conjugated hyperbilirubinemia in first weeks of life, or transient elevations of aminotransferases
  - Hematologic abnormalities
    - ◆ Thrombocytopenia
    - ◆ Neutropenia, lymphopenia, and hemolytic anemia
- Mother
  - 50% of women with a child w/ NLE are **asymptomatic at time of child's birth**
    - ◆ Half of mothers who are initially asymptomatic later develop Sjogren's syndrome or SLE
- Histology
  - Same as SCLE
  - DIF: (+) LBT in 50%
- Laboratory testing
  - Autoantibodies
    - Anti-Ro/SS-A antibodies (99%)
    - Anti-La/SS-B and anti-U1RNP antibodies may be found in combination with anti-Ro/SS-A antibodies (rarely present alone)
  - ↑LFTs
  - Hematologic cytopenias (mainly thrombocytopenia)
- Treatment
  - Skin disease
    - Sun protection + topical corticosteroids
  - Cardiac disease
    - In utero:
      - ◆ **Prenatal systemic corticosteroids** may ↓risk of developing congenital heart block
        - ➔ Does not decrease rate of cutaneous NLE, however
      - ◆ **Hydroxychloroquine throughout pregnancy** → ↓risk of a child w/ cardiac NLE for women w/ SLE and anti-Ro/SS-A (+) women with a previous child affected by NLE
    - Neonatal:
      - ◆ Once complete heart block occurs, it is **irreversible**
      - ◆ **Pacemaker** required for heart block in two thirds of pts w/ cardiac NLE

- Hematologic and LFT abnormalities
  - Usually no treatment is needed
- Prognosis/clinical course
  - Children with NLE may be at ↑risk of developing SLE or autoimmunity later in life
  - Skin disease
    - Lesions **resolve without scarring** by ~6 months (as maternal antibodies clear from neonatal circulation)
    - **Residual atrophy, dyspigmentation and telangiectasias** persist for months to years
  - Cardiac disease
    - Low-grade AV blocks are reversible and sometimes normalize without therapy
    - **Complete (third degree) heart block is irreversible**
    - **Cardiac NLE has 20%–30% mortality rate**
  - Hematologic and LFT abnormalities
    - Transient with spontaneous resolution within 4 to 6 months

MCQ  
Promotion 2016

### Complement deficiencies

- Epidemiology
  - Primary C2 deficiency
    - **Most common** hereditary complement disorder
    - Only 10%–20% with homozygous C2 deficiency will develop SLE (**low risk**)
      - ◆ However, because C2 deficiency is so much more common compared to other early complement deficiencies, C2 deficiency is the **most common cause of complement deficiency-associated SLE**
  - Primary C1q and C4 deficiencies
    - Homozygous deficiencies are **very rare**, but when present are associated with a **very high risk** of developing autoimmune disease
    - **SLE risk with homozygous mutations: C1q (~90%) > C1r/s > C4 > C2 (10%–20%)**
- Pathogenesis
  - UV-damaged apoptotic keratinocytes express autoantigens (esp. Ro/SSA) on cell surface
  - Early components of complement normally help clear out these apoptotic keratinocytes
  - **Deficiencies in early components (C1, C4, C2) of classic complement pathway → impaired phagocytic clearance** of apoptotic bodies containing high levels of autoantigens → loss of immune tolerance and autoantibody-mediated inflammation
- Clinical
  - Deficiency of any early classical complement component (C1, C2, C4) is a/w **↑risk for SLE and infections w/ encapsulated bacteria**
  - C2 deficiency-associated SLE (most common but least severe):
    - Adult onset (avg 30 yo)
    - F > M
    - SLE w/ less severe systemic disease (e.g., mild or absent renal disease)
    - Prominent photosensitivity and SCLE lesions
    - ↑bacterial infections w/ encapsulated bacteria, especially *S. pneumonia*

- C1q/r/s and C4 deficiency-associated SLE (less common but more severe)
  - Childhood onset
  - **Severe, recalcitrant renal disease**
  - Photosensitivity with CCLE or SCLE
  - Palmoplantar keratoses (C4 deficiency only)
  - ↑risk of infection with encapsulated bacteria and candida
- Anti-C1q autoantibodies (acquired)
  - Arise in 30%–50% of SLE patients, **a/w lupus nephritis**
  - Seen in ~100% of pts w/ **hypocomplementemic urticarial vasculitis**
- Laboratory findings
  - Low or absent ANA titers
  - Anti-Ro/SS-A antibodies in majority
  - ↓complement levels (screening test is CH50, which is markedly decreased)

### Acute cutaneous lupus (ACLE)

- 60% of SLE patients develop a malar rash
- Of the three major cutaneous lupus subtypes, **ACLE is most strongly a/w SLE**
- Classically p/w localized (**malar**) erythema = “**butterfly rash**” (Fig. 3-38); a **transient** eruption following sun exposure lasting hours to weeks
  - Classically involves the nasal bridge and bilateral malar eminence, **sparing the melolabial folds** (in contrast to the facial erythema of dermatomyositis), but may also involve the forehead, periorbital areas, and sides of neck
  - Morphology ranges from mild erythema to edematous lesions
  - Lesions may develop scaling, papules, erosions, **poikiloderma**, atrophy, or dyspigmentation that can help distinguish it from other facial rashes
  - Malar discoid lesions do not count as a “butterfly rash”
- Butterfly rash may occasionally be accompanied by a more generalized photodistributed eruption involving the **V-neck, upper back, extremities**, and dorsal hands,



**Figure 3-38.** Acute cutaneous lupus erythematosus (ACLE). The facial erythema often referred to as a “butterfly rash” may be variable. The presence of small erosions can aid in the clinical differential diagnosis (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- classically **sparing the knuckles** (in contrast to the confluent macular violaceous erythema of DM)
- Histopathology: vacuolar interface dermatitis, dermal edema, and **sparse** perivascular lymphocytic infiltrate limited to upper dermis
  - Lacks follicular plugging and other dermal changes
- DIF: (+) LBT
- Laboratory tests: **ACLE is highly a/w SLE → perform same lab studies as in SLE** to search for end-organ damage
- Treatment: skin lesions of ACLE respond to treatment for systemic symptoms; for recalcitrant skin disease, refer to treatment algorithm presented in DLE section
  - Cutaneous flares tend to correlate w/ systemic disease activity

### Other rare cutaneous lupus variants

#### Bullous SLE

- Epidemiology
  - Female predominance
  - Predominately **African Americans**
- Pathogenesis
  - Antibodies against NC1 and NC2 domains of **type VII collagen (same as EBA)**
  - a/w HLA-DR2
- Clinical
  - By definition, **patients must meet ACR criteria for diagnosis of SLE** in order to term it “bullous SLE”
  - Widespread, symmetric eruption of **tense, subepidermal bullae** on erythematous-to-urticarial base (Fig. 3-39)
  - Involves both sun-exposed and non-exposed areas
  - Typical locations: face, neck, upper trunk, and proximal extremities
    - Also, commonly involves mucosa
  - Systemic symptoms same as SLE
- Histopathology
  - **Subepidermal bulla with neutrophils at DEJ** and in dermal papillae
  - DIF: continuous granular to linear deposition of IgG, IgM, IgA and/or C3 along BMZ



**Figure 3-39.** Bullous lupus erythematosus. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- Laboratory testing
  - Salt-split skin: **dermal reactivity** on salt-split skin
  - ELISA: autoantibodies to collagen VII
  - **ANA (+) in ~100%**
    - Frequently positive for dsDNA, Sm, Ro/SSA, and La/SSB
  - Also, perform standard labs as per SLE to search for end-organ damage
- Treatment
  - **Dapsone (ToC)** → dramatic response within 1–2 days
    - Differentiates bullous SLE from EBA!
  - Immunosuppressant meds may be needed for recalcitrant disease
- Prognosis/clinical course
  - Often a/w systemic lupus flare
  - Lesions of bullous LE respond dramatically to dapsone with cessation of new lesions and healing over a few days

#### Rowell's syndrome

- Targetoid lesions clinically resembling EM, arising in setting of ACLE, SCLE, or DLE; **typically Ro/SSA (+)**

#### Toxic epidermal necrolysis-like lupus erythematosus

- Triggered by excessive UV exposure in patients with preexisting ACLE or SCLE

## Systemic lupus erythematosus (SLE)

#### Epidemiology

- 80% of SLE patients will have skin findings
  - ACLE is the cutaneous phenotype most strongly a/w systemic lupus, but pts with any form of cutaneous lupus may develop SLE
  - Also, pts with SLE may have any combination of the various forms of cutaneous lupus
- Female predominance
- **African Americans have a 4-fold ↑incidence**, earlier age of onset, and higher mortality

#### Pathogenesis

- Type I interferon-inducible gene signature in peripheral blood leukocytes
  - Other major cytokines: B-lymphocyte stimulator (BLys), IL-6, IL-17, IL-18, and TNF- $\alpha$
- Phagocytic defect of monocytes and macrophages to clear apoptotic cells
- Autoreactive B-cells undergo clonally selective specificity, maturation, and class switching specific for DNA and nuclear antigens
- Genetics
  - Strong genetic component
  - Susceptibility loci conferring the highest risk for SLE:
    - Genes encoding **early complement components** (C1, C2, C4)
    - TREX1
    - ITGAM
- Environmental triggers: **sunlight, cigarettes, infections, vitamin D deficiency, estrogen**

#### Clinical

- SLE diagnostic criteria (ACR criteria for SLE)
  - Need to satisfy **four items** (at least one clinical and one immunologic item) **OR** have biopsy-proven nephritis compatible w/ SLE in the presence of ANA or anti-dsDNA antibodies ([Table 3-13](#))
- Cutaneous manifestations of SLE
  - **Lupus-specific skin findings:**
    - ACLE
    - SCLE
    - CCLE
    - Rowell syndrome
    - TEN-like LE
    - Bullous SLE
  - **Non-specific skin findings suggestive of SLE:**
    - Diffuse non-scarring alopecia
    - Periungual telangiectasias and erythema
      - ◆ Dermoscopy: **"wandering" dilated glomeruloid loops** (in contrast, DM and SSc both have symmetric dilation and dropout of vessels; Osler-Weber-Rendu has ectasia of half of the capillary loop)
    - Non-specific mucosal ulcers
    - Vasculitis:
      - ◆ LCV (most common)
      - ◆ Urticarial vasculitis (especially HUV)
      - ◆ Medium vessel PAN-like lesions
      - ◆ PNGD/IGDA
    - Cutaneous signs of antiphospholipid syndrome (APLS):
      - ◆ Livedo reticularis (LR + ischemic strokes = **Sneddon syndrome**)
      - ◆ Atrophie blanche-like lesions
      - ◆ **Degos'-like lesions**
      - ◆ Ulcerations
      - ◆ Purpura fulminans and retiform purpura due catastrophic APLS
    - Papulonodular mucinosis
      - ◆ Asymptomatic skin colored to red papules w/ central depression and pigmentation; favors V-neck, upper chest/back, and upper extremities
    - Others:
      - ◆ Secondary Raynaud's, **multiple eruptive dermatofibromas**, and calcinosis cutis
- SLE and pregnancy
  - Course may be stable, worsen, or improve
  - Patients w/ lupus nephritis are at ↑risk of complications
  - Postpartum period is highest risk
  - Fetal complications
    - Preterm birth
    - Preeclampsia, especially w/ lupus nephritis
    - Anti-cardiolipin antibodies → **↑risk of fetal loss**
    - **Neonatal LE** in patients w/ **anti-Ro/SS-A** and **anti-La/SS-B**
  - Management in pregnancy
    - Continuation of hydroxychloroquine and low dose steroids
    - Consider azathioprine
    - Anticoagulation for APLS



**Table 3-13.** The American College of Rheumatology 1982 Revised Criteria for Classification of Systemic Lupus Erythematosus\*

Criterion	Definition
Malar rash	Fixed erythema (flat or raised) over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	a) <b>Pleuritis</b> – convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion OR b) <b>Pericarditis</b> – documented by ECG, rub, or evidence of pericardial effusion
Renal disorder	a) Persistent <b>proteinuria</b> greater than 0.5 g/day or greater than 3+ if quantitation not performed OR b) <b>Cellular casts</b> – may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	a) <b>Seizures</b> – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) <b>Psychosis</b> – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis or electrolyte imbalance
Hematologic disorder	a) <b>Hemolytic anemia</b> with reticulocytosis OR b) <b>Leukopenia</b> – less than 4000/mm <sup>3</sup> total WBC on two or more occasions OR c) <b>Lymphopenia</b> – less than 1500/mm <sup>3</sup> on two or more occasions OR d) <b>Thrombocytopenia</b> – less than 100 000/mm <sup>3</sup> in the absence of offending drugs
Immunologic disorder	a) <b>Anti-DNA antibody to native DNA</b> in abnormal titer OR b) <b>Anti-Sm</b> : presence of antibody to Sm nuclear antigen OR c) Positive finding of <b>antiphospholipid antibodies</b> based on: (1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies; (2) a positive test result for lupus anticoagulant using standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome

ECG, electrocardiogram; Sm, Smith; WBC, white blood cell

\*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

### Histopathology

- Please refer to sections on types of lupus-specific skin lesions

### Laboratory testing

- Routine labs: ↑inflammatory markers (ESR and CRP), hemolytic anemia (Coombs positive), leukopenia or lymphopenia, thrombocytopenia, proteinuria, and hematuria
- Complement abnormalities: ↓total complement levels (CH50), autoantibodies against C1q (a/w severe SLE nephritis and hypocomplementemic urticarial vasculitis)
- Serologies:
  - ANA (99%)
  - Anti-ssDNA antibodies
    - Neither sensitive nor specific for SLE
  - Anti-dsDNA (60%)
    - Not sensitive, but **highly specific** (95%) for SLE
    - Useful in **monitoring** disease activity (esp. **lupus nephritis**)
    - Correlates strongly w/ **LBT from sun-protected skin**
    - Likely contribute to pathogenesis of disease

- **Anti-Smith antibodies** (10%–30%)
  - Not sensitive, but **highly specific** for SLE
- Anti-U1RNP (50%)
  - Lower titers in SLE compared to MCTD (most important association)
- Anti-Ro/SS-A antibodies (50%)
- Anti-histone antibodies
  - **Drug-induced SLE** (>95%)
- Anti-RNP (ribosomal P) antibodies
  - High specificity but low sensitivity for SLE
  - a/w **neuropsychiatric SLE**
  - Not currently used in clinical practice
- Antiphospholipid antibodies
  - Anti-β2-glycoprotein IgM/IgG/IgA
  - Anti-anticardiolipin IgM/IgG/IgA
  - Lupus anticoagulant activity

### Treatment

- Mild active disease (no life-threatening visceral organ involvement): **hydroxychloroquine** and NSAIDs
- Moderate-severe active disease lacking renal involvement: prednisone + steroid-sparing agent (azathioprine, MTX, or MMF)
- Severe active disease w/ renal involvement: **prednisone (high dose) + pulsed IV cyclophosphamide** or MMF

- Moderate-severe recalcitrant disease:
  - **Rituximab:**
    - May be beneficial for moderate to severe disease w/ lupus nephritis, especially in African Americans and Latinos, but has not met primary end points in clinical trials
  - **Belimumab**
    - A monoclonal human antibody that inactivates BlyS (B-lymphocyte stimulator) causing apoptosis and inhibition of B-cell maturation
    - Two trials have supported the efficacy of belimumab in recalcitrant SLE, but skin disease was not assessed independently

#### Prognosis/clinical course

- Childhood onset has a higher risk of lupus nephritis and mortality
- 10 year survival: ~90%
- Most common causes of death:
  - First 5 years: inflammatory lesions of SLE and infection
  - Beyond 5 years: arterial (e.g., MI) and venous (i.e., DVT/PE) **thromboses**
    - ↑risk of thrombosis w/ anticardiolipin antibodies and OCPs

#### Drug-induced SLE (DILE)

- Lupus-like syndrome related to continuous drug exposure (**usually >1 yr after drug initiation**) that typically resolves within 4 to 6 weeks of discontinuation of offending drug
- Serologically characterized by (+) **anti-histone antibodies (>95%)** and (–) **dsDNA autoantibodies**
  - Positivity for antinuclear antibodies may persist for up to 12 months, even in absence of clinical symptoms!
- Patients generally do not meet ACR criteria for SLE
- DILE typically **lacks skin findings** and has milder systemic involvement (**lacks renal and CNS findings**) than idiopathic SLE
- Most common clinical findings:
  - **Arthritis/arthralgia (90%)**
  - Myalgia (50%)
  - Serositis (pericarditis, pleuritic)
  - Fever and weight loss
- Most important implicated drugs:
  - **High risk:** procainamide, hydralazine
    - a/w slow acetylators
  - **Medium and low risk:** quinidine, methyldopa, isoniazid, chlorpromazine, D-penicillamine, propylthiouracil, PUVA, minocycline, **TNF-α inhibitors** (infliximab and etanercept > adalimumab)
    - D-penicillamine may “unmask” true SLE
    - Minocycline differs from classic DILE:
      - ◆ Often negative for anti-histone antibodies
      - ◆ (+) ANCA against MPO or elastase
    - **TNF-α inhibitors differ from classic DILE:**
      - ◆ anti-dsDNA antibodies frequently positive (> anti-histone)
      - ◆ ↑↑↑skin involvement (malar rash, photosensitivity, SCLE and DLE lesions)

MCQ  
Promotion  
2016

#### Lupus-related diseases

##### Jessner's lymphocytic infiltrate of skin

- Epidemiology
  - Primarily middle-aged adults
  - No gender predilection
- Pathogenesis
  - Photosensitive eruption
  - Possibly a variant of LE, on a spectrum w/ tumid LE and REM
- Clinical
  - Red papules or plaques (often **annular w/ central clearing**)
  - Absent epidermal changes
  - Typical locations: **head, neck, and upper back**
  - Duration: weeks to months
  - No systemic manifestations
- Histopathology
  - Similar to tumid LE and REM, but with a predominance of suppressor CD8+ T-cells and **↓mucin**
  - Absent interface dermatitis
  - Superficial and **deep dense PV/PA lymphocytic infiltrate**
  - DIF: negative
- Laboratory testing
  - No associated laboratory abnormalities
- Treatment: sun protection, antimalarials
- Prognosis/clinical course: resolves spontaneously without sequelae

##### Reticular erythematous mucinosis

- Middle-aged females often w/ **history of tanning bed use**
- Likely variant of LE, on spectrum w/ tumid LE
- p/w persistent, **photoaggravated** (UVA and UVB) eruption consisting of erythematous papules or plaques on **middle of chest/back**, typically in a reticular configuration
- Exacerbating factors: OCPs, menses, pregnancy, heat, and sweating



**Figure 3-40.** Lymphocytic infiltrate of Jessner. Annular erythematous plaque on the face. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Histopathology: same as tumid lupus; DIF negative (most cases)
- Laboratory testing: no associated laboratory abnormalities
- Treatment: sun protection, antimalarials → resolution within 4 to 8 weeks w/ antimalarials

## Other autoimmune connective tissue diseases and sclerosing dermopathies

### Dermatomyositis (DM)

#### Epidemiology

- Female predominance
- **Bimodal peaks:** childhood (5–14 yo) and adulthood (45–65 yo)

#### Pathogenesis

- Environmental factors (e.g., **malignancy**, viral infections) trigger an immune-mediated process in susceptible individuals
- Genetic predisposition:
  - Polymorphisms in various HLA alleles
  - TNF- $\alpha$ 308A polymorphism (a/w juvenile DM) →  $\uparrow$ thrombospondin-1 (a potent anti-angiogenic factor) →  $\uparrow$ occlusion of capillaries
- Drug-induced dermatomyositis:
  - Hydroxyurea (most common, >50%)
  - Statins
  - D-penicillamine
  - Cyclophosphamide
  - BCG vaccine
  - TNF- $\alpha$  inhibitors

#### Clinical features

- Muscle disease:
  - Slowly progressive, **symmetric proximal muscle weakness** (extensors > flexors)
  - Generally **lacks muscle pain** (myalgias)
  - Typically affects shoulders, hip girdle, and neck flexors → **difficulty walking up stairs**, standing up from sitting position, or **brushing hair**
  - Esophageal/oropharyngeal muscles → dysphagia, aspiration pneumonia
  - Cardiac disease (common)
    - Mostly subclinical EKG abnormalities
    - Clinically overt disease (CHF, complete heart block, dangerous arrhythmias, and coronary artery disease) is rare but life-threatening
  - Diaphragm weakness (rare but life-threatening)
- Classic skin findings:
  - **Gottron's papules (pathognomonic)**
    - Lichenoid papules **overlying knuckles** (> other extensor joints) (Fig. 3-41)
    - Less common than Gottron's sign (macular erythema overlying joints)
  - Symmetric confluent macular violaceous erythema (CMVE)
    - Facial erythema w/ **malar involvement**, usually involving the melolabial folds (vs lupus)



**Figure 3-41.** Dermatomyositis – Gottron's papules. Obvious accentuation of skin lesions over the metacarpophalangeal (MCP) joints with coalescence of pink-violet lichenoid papules. Courtesy, Julie V Schaffer, MD. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)



**Figure 3-42.** "Mechanic's hands" in dermatomyositis. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

- Eyelids = **heliotrope sign** +/- periorbital edema
  - ◆ Arises as a result of inflammation of underlying orbicularis oculi muscle, NOT the skin!
- Lateral thigh = **Holster sign**
- Overlying joints = **Gottron's sign**
  - ◆ Elbows, knees, DIP, PIP, and MCP joints
- Overlying extensor tendons of hands and forearms = linear extensor erythema
- Photodistributed CMVE or **poikiloderma** (hyperpigmentation, hypopigmentation, telangiectasias, and atrophy)
  - Chest/upper back = "**V-sign**" (aka "**Shawl sign**")
- Other common skin findings:
  - **Mechanic's hands**
    - Rough, hyperkeratosis and fissuring of the lateral and palmar side of fingers, usually more radial digits involved (Fig. 3-42)
    - Strongly a/w **anti-synthetase syndrome**
  - Nail changes
    - "**Ragged**" cuticles
    - Proximal nailfold w/ dilated capillary loops alternating with areas of vessel dropout (Fig. 3-43)
    - Periungual erythema





**Figure 3-43.** Cuticular hypertrophy, splinter hemorrhages, and periungual telangiectases in a patient with dermatomyositis. (From Callen JP, et al. Dermatological Signs of Internal Disease 4th ed. Elsevier. 2009)

- Pruritus – often severe (especially on scalp)
  - Helps to differentiate from lupus and psoriasis, which do not tend to itch
- Psoriasiform dermatitis of scalp
- Less common skin findings:
  - Calcinosis cutis
    - Much more common in Juvenile DM (25%–70%) than adults (<20%)
      - ◆ a/w anti-p140 (NXP-2) autoantibodies in JDM
    - Favors elbows, knees, and buttocks
    - a/w fingertip ulcers and prolonged course
  - Palmar papules
    - Erythematous palmar papules or macules +/- overlying hyperkeratosis/ulceration; **painful** (unlike Gottron's papules)
    - a/w **anti-CADM-140** antibodies
  - Clinical features overlapping w/ PRP (Wong-type dermatomyositis)
  - **Vasculitis** (never a good sign!) **MCQ**
    - In adults → a/w **malignancy** **Promotion 2016**
    - **JDM** w/ severe systemic vasculitis = **Banker variant JDM**
      - ◆ Cutaneous ulcerations, muscle infarction, GI involvement (hemorrhage, ulceration, perforation), **widespread calcinosis**, and a **severe course** w/ poor response to therapy
  - Others: **flagellate erythema**, acquired lipodystrophy, hypertrichosis, Raynaud's phenomenon, and erythroderma
- Other common (non-muscular) systemic findings:
  - Pulmonary disease (15%–65%)
    - p/w diffuse **interstitial lung disease (ILD)** of varying severity
    - Rapidly progressive ILD → a/w **anti-synthetase** and **anti-CADM-140** autoantibodies
  - Arthralgia and/or non-erosive arthritis

#### Classification (Box 3-5)

- Adult onset DM
  - Classic DM
    - Slowly progressive symmetric, proximal muscle weakness w/ classic skin findings

#### Box 3-5. Dermatomyositis Classification

##### Adult-onset

- Classic DM
- Cancer-associated myositis (CAM)
- DM overlap syndrome
- Clinically amyopathic DM (CADM)
  - Amyopathic DM
  - Hypomyopathic DM

##### Juvenile DM

- Classic DM
- Clinically amyopathic DM (CADM)
  - Amyopathic DM
  - Hypomyopathic DM

- Clinically amyopathic DM (amyopathic or hypomyopathic)
  - Classic skin findings **without clinical muscle disease**
  - a/w **ILD**
  - a/w **anti-CADM-140 (MDA5)** autoantibodies
- Cancer-associated myositis
  - May p/w Classic DM or CADM
  - Associated with: **↑age** (fifth to sixth decades most common), **rapid disease onset**, **skin necrosis**, periungual erythema, markedly elevated ESR or CK, **anti-p155/140 autoantibodies**, lack of anti-synthetase syndrome features, and lack of Raynaud's phenomenon
  - Most common cancers:
    - ◆ **Ovarian** (classic exam answer!) and **GI** (colon > other) cancer are overrepresented
    - ◆ Nasopharyngeal carcinoma overrepresented in Asians
    - ◆ Others: breast, lung, pancreatic, and non-Hodgkin's lymphoma
  - Timing:
    - ◆ Malignancy may be discovered before, after, or at the same time as the diagnosis of DM
    - ◆ Cancers diagnosed before DM precede diagnosis by ≤2 years
    - ◆ **Most cancers are detected within 1–2 years of DM diagnosis**
    - ◆ **Risk for most cancers returns to normal 5 years after diagnosis** (exceptions = pancreatic and colorectal cancers → risk remains elevated beyond 5 years)
- **Anti-synthetase syndrome** (boards favorite!)
  - Acute disease onset
  - Constitutional symptoms
  - Raynaud's phenomenon
  - **Mechanics hands**
  - Non-erosive arthritis
  - **ILD**
    - Anti-synthetase autoantibodies
- DM overlap syndromes
  - Definition: DM + other CTD
  - Autoantibodies suggestive of overlap
    - ◆ Anti-U1-RNP = mixed CTD
    - ◆ Anti-Ku = polymyositis overlapping with either SLE, Sjogren syndrome, or scleroderma



- ◆ Anti-PM/Scl (PM-1) = DM/PM + scleroderma ("sclerodermatomyositis")
- Juvenile DM
  - DM in patients <16 yo (average 7 yo); F > M (2–5:1)
  - JDM is **not** a/w ↑risk malignancy!
  - Important autoantibodies in JDM (some antibodies may have different associations in kids vs adults):
    - anti-CADM-140 (MDA5) → a/w ILD in kids
    - Anti-p155/140 → a/w extensive skin disease in kids but no increase in malignancy
    - **Anti-p140** (recognizes nuclear matrix protein NXP-2) → a/w **calcinosis and contractures** in kids
  - Variants:
    - **Classic JDM (Brunsting variant):**
      - ◆ Most common (90%)
      - ◆ Gradual onset of classic skin and muscle disease
      - ◆ Frequent calcinosis cutis → favors sites of trauma (fingers, elbows, knees, and buttocks); may ulcerate
      - ◆ Corticosteroid responsive
    - **Vasculopathic/ulcerative JDM (Banker variant):**
      - ◆ Fortunately rare (<10%)
      - ◆ Rapid onset of severe muscle disease
      - ◆ Severe vasculitis w/ cutaneous ulcerations, livedo reticularis, severe periungual capillary alterations, muscle infarction, and GI ulceration, pneumatosis, and perforation
      - ◆ Recalcitrant to corticosteroid therapy, **poor prognosis**

#### Histopathology

- **Subtle** vacuolar interface w/ rare scattered necrotic keratinocytes, epidermal atrophy, ↑BMZ material, **sparse** PV/PA lymphocytic inflammation, and **massive dermal mucin** deposition
- DIF (non-specific): granular deposition of immunoglobulins and C3 at DEJ (50%) and on colloid bodies

#### Laboratory testing

- (+) ANA (40%)
- ↑↑muscle enzymes (CK, aldolase)
  - CK is a more sensitive marker of muscle involvement in DM, but there can be a discordant elevation in aldolase w/ normal CK levels
- EMG
- Imaging: MRI or contrast induced US
- Muscle biopsy (gold standard)
- Myositis specific autoantibodies (Table 3-11)
  - Abbreviations used in Table 3-11: CADM (clinically amyopathic DM); CAM (cancer-associated myopathy); MDA5 (melanoma differentiation-associated gene 5); NA (not applicable); TIF1-γ (transcriptional intermediary factor 1-γ)

#### Treatment

- Skin-limited disease:
  - First line: photoprotection, topical corticosteroids and calcineurin inhibitors +/- antimalarials
    - Caution w/ antimalarials → ↓efficacy and ↑risk of cutaneous drug eruptions in DM, relative to lupus

- Second line: MTX, MMF, IVIG, and other immunosuppressive meds
- Calcinosis cutis: diltiazem, surgical excision; early aggressive treatment of JDM → decreased risk of calcinosis cutis
- Disease monitoring:
  - Re-check muscle enzymes and clinical exam q 2 to 3 months → if muscle disease arises → initiate systemic steroids
  - Physical exams q 4 to 6 months to screen for malignancy for the first 2–3 years after diagnosis
- Skin + muscle disease
  - First line: **systemic corticosteroids**, MTX, and azathioprine
- Second line: IVIG and other immunosuppressive meds

#### Prognosis/clinical course

- Adult DM
  - **Most common causes of death** = malignancy, ischemic heart disease, and pulmonary complications
- Juvenile DM
  - Prior to the availability of corticosteroids, JDM had poor prognosis: one third of children died, one third had a progressive crippling course, and one third had chronically active disease
  - With corticosteroid therapy, **majority have favorable outcomes** with minimal to no sequelae
  - Delayed or inadequate corticosteroid therapy = important predictor of poor outcome and chronic course

#### Additional boards factoids

- Drug-induced DM is separated into **hydroxyurea-induced** and **non-hydroxyurea-induced** groups:
  - Hydroxyurea-induced DM: much longer latency period (**average 60 months**) after drug initiation; **myositis never seen** (0%); only 16% have (+) ANA
  - Non-hydroxyurea-induced DM: occurs within 2 months after drug initiation; **80% have muscle weakness/myositis**; ANA usually (+) (54%)
- Both groups have pathognomonic skin lesions of DM (heliotrope rash, Gottron's papules), and may have (+) ANA
- Both forms resolve within 1 to 2 months of drug discontinuation

### Sjogren syndrome (SjS)

#### Epidemiology

- Mean age of onset: 30–50 yo
- **Strong female predominance** (F:M = 9:1)
- One third with extraglandular disease
- May be primary or secondary to other CTDs (RA, SLE, SSC)

#### Pathogenesis

- Lymphocytic infiltration of exocrine glands (**lacrimal and salivary glands**)
- Frequently a/w **anti-Ro/SS-A** (60%–70%) and **anti-La/SS-B** (20%–40%) antibodies
  - (+) autoantibodies a/w ↓age of onset and ↑risk of extraglandular disease

- Germline abnormality of TNFAIP3 → ↑risk of antigen-driven **B-cell lymphomas**

### Clinical

- ACR diagnostic criteria
  - In individuals with signs/symptoms suggestive of SjS, at least two of three objective features are required for diagnosis:
    - Anti-SSA/Ro and/or anti-SSB/La OR positive RF and ANA titer  $\geq 1:320$
    - Positive labial salivary gland biopsy
    - Keratoconjunctivitis sicca w/ ocular staining score  $\geq 3$

### Symptoms and signs

- Mucous membranes
  - **Mucosal xerosis occurs later in disease course after >50% of glands destroyed**, so early disease may present with only non-specific symptoms of fatigue, arthralgias, and myalgias
  - **Xerophthalmia (aka keratoconjunctivitis sicca):**
    - Due to involvement of lacrimal gland
    - Symptoms: dry eyes, pain, photophobia, or foreign body sensation
    - Complications: keratitis, corneal ulceration, and recurrent infections
    - Signs of impaired lacrimal gland function (uncommonly performed)
      - ◆ **Schirmer test:** Whatman paper wick fold over lower eye (tear film migrates <5 mm in 5 min = positive test)
      - ◆ **Rose Bengal test:** measures quality of ocular surface epithelium
  - **Xerostomia:**
    - Due to involvement of major (parotid and submandibular) and minor salivary glands
    - Symptoms: **dry mouth**, sore/burning mouth/lips, dysphagia, and transient bilateral or unilateral **swelling of parotid** and submandibular glands
      - ◆ If persistent swelling → consider workup for lymphoma
    - Complications: perlèche, thrush, dental caries, and severe GERD
    - Tests for impaired salivary gland function/flow rate: salivary gland scintigraphy, sialometry or parotid sialography (uncommonly performed)
  - Vaginal xerosis
    - Symptoms: dyspareunia, dryness, and burning
    - Complication: bacterial and *Candida* overgrowth
- Skin
  - Xerosis/pruritus
    - **Most common skin finding**
  - **Vasculitis (most important skin finding because of associated complications)**
    - May present as small to large vessel vasculitis (any size)
      - ◆ **Classic LCV** (+/- cryoglobulins)
      - ◆ **Urticarial vasculitis** (either hypo- or normocomplementemic)
      - ◆ **PAN-like** subcutaneous nodules and ulcers

- Vasculitis is a/w:
  - ◆ **Systemic involvement** (arthritis, peripheral neuropathy, Raynaud's phenomenon, and renal involvement)
  - ◆ Positive serology (**anti-Ro/SS-A**, ANA, and RF)
  - ◆ ↑ESR
  - ◆ **Lymphoma**
  - ◆ **↑mortality**
- Annular erythema of Sjogren syndrome (AE-SS)
  - Clinically similar to SCLE; mostly in Japanese
- Raynaud's phenomenon
- Purpura with capillaritis on histology
- Waldenstrom's hypergammaglobulinemic purpura
- Erythema nodosum
- Livedo reticularis
- Systemic
  - Neurologic
    - Neuropathy: distal, symmetric, painful sensory or sensorimotor polyneuropathy (most common)
    - Other: memory loss, hearing loss, and Devic syndrome (aka neuromyelitis optica; variant of MS with optic neuritis and transverse myelitis)
  - Arthritis
    - Usually polyarticular, chronic progressive
    - May be asymmetric
    - Ankles and knees most commonly involved
  - **Lymphomas (most severe complication)**
    - 19-fold ↑risk of **non-Hodgkin lymphomas**, predominately extranodal marginal zone B-cell lymphomas (aka MALT = mucosa-associated lymphoid tissue), usually involving organs in which SjS is most active, such as **major salivary glands (most common)**
  - Glomerulonephritis
  - Pregnancy
    - ↑**risk of neonatal LE** in mothers with anti-Ro/SSA antibodies

### Histopathology

- Salivary gland histology
  - Presence of focal lymphocytic sialoadenitis with two or more aggregates of 50 or more lymphocytes per 4 mm of glandular tissue
  - A mixture of T-cells and B-cells with a normal CD4:CD8 ratio

### Laboratory testing

- Autoantibodies:
  - **Anti-fodrin** (70%), most sensitive and specific test
  - **Anti-Ro/SSA** (60%–70%)
  - **Anti-La/SSB** (20%–40%)
- Other: ↑ESR/CRP, hypergammaglobulinemia, anemia, leukopenia, and mixed cryoglobulinemia

### Treatment

- Treatment primarily symptomatic
  - Xerophthalmia
    - Preservative-free artificial tears during the day
    - Lubricating ointments at night

- Punctae occlusion: plugs placed in the lacrimal puncta to ↑ accumulation of tear film
- Cyclosporine (0.05%) eye drops BID for moderate to severe dry eyes
- Xerostomia
  - Artificial saliva (not usually tolerated well)
  - Frequent water ingestion
  - For patients with residual salivary gland function
    - ◆ Salivary stimulants (e.g., acid-free and sugar-free gum containing xylitol and sorbitol)
    - ◆ Sialogogue therapy: pilocarpine and cevimeline
  - Meticulous dental hygiene and fluoride treatments to prevent dental caries
  - Avoid alcohol, smoking, and low pH drinks (e.g., soda)
- Immunosuppressive meds only used for severe extraglandular systemic involvement
- Rituximab may be considered for refractory cases

#### Prognosis/clinical course

- On average, mortality rate similar to general population, but is two to three times higher in patients with extraglandular disease
- **Adverse prognostic factors a/w ↑ mortality:** hypocomplementemia, cryoglobulinemia, vasculitis, and lymphoproliferative diseases

### Relapsing polychondritis

#### Epidemiology

- Age of onset 20–60 yo
- a/w second autoimmune disease in 30%
- M = F

#### Pathogenesis

- Intermittent episodes of inflammation of articular and non-articular cartilage → chondrolysis and structural collapse
- Autoantibody titers against **type II collagen** correlate w/ disease activity, but are only present in 30%–50% of patients
- a/w **HLA-DR4**

#### Clinical

- Diagnostic criteria: three of six criteria required for diagnosis
  - Recurrent chondritis of both auricles (90%)
    - Presenting sign in 25%
    - Bright red, swollen, tender cartilaginous portion of ears, and **sparing earlobes**
    - Recurrent episodes leading to floppy (“cauliflower”) ears (Fig. 3-44)
    - May lead to conductive **hearing loss** due to collapse and edema of external auditory canal
  - Chondritis of nasal cartilages (70%)
    - Nasal congestion, rhinorrhea, crusting, epistaxis, decreased sense of smell
    - May lead to **saddle nose deformity** (more common in females and younger patients)



**Figure 3-44.** Relapsing polychondritis characteristically involves cartilaginous portions of the ear but spares the lobe. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- Non-erosive inflammatory polyarthritis (50%–75%)
  - Episodic, migratory, asymmetric, non-erosive oligo- or polyarthritis, typically effecting knees, wrists, MCPs, and PIPs
  - Peripheral arthritis has worse prognosis
  - Other joints involved:
    - ◆ Costochondritis
    - ◆ Sternoclavicular and sternomanubrial joints
- Inflammation of ocular structures (65%)
  - Any part of eye affected → conjunctivitis, corneal ulcers, scleritis, iritis, or uveitis
- Chondritis of respiratory tract (laryngeal/tracheal/bronchial cartilages)
  - **Hoarseness, wheezing, coughing, dyspnea, and subglottic strictures**
  - May → airway collapse/obstruction and ↑ risk of **pneumonia (#1 cause of mortality)**
- Cochlear and/or vestibular damage
  - Neurosensory hearing loss, tinnitus, and vertigo
- Other clinical findings
  - Cardiovascular
    - Valvulopathy: usually mitral or aortic valve regurgitation
    - Vasculitis
      - ◆ Portends worse prognosis (second most common cause of death)
      - ◆ Ranges from cutaneous small vessel vasculitis to large vessel vasculitis w/ aneurysmal dilation, most commonly involving abdominal and thoracic aorta
  - Non-specific skin/mucosal findings (35%)
    - Aphthous ulcers, erythema nodosum

- Associated with:
  - Other autoimmune diseases
    - **MAGIC syndrome** (Mouth And Genital ulcers with Inflamed Cartilage) = **Behcet's disease + relapsing polychondritis**
  - Hematologic malignancies, most commonly myelodysplastic syndrome

#### Histopathology

- Early: cartilaginous neutrophilic infiltrate
- Later: lymphoplasmacytic infiltrates with replacement of cartilage by granulation tissue and fibrosis

#### Laboratory testing

- Normochromic/normocytic anemia (a/w worse prognosis), ↑ESR/CRP, mild leukocytosis, ↑Cr/BUN and microscopic hematuria (if vasculitis affects kidneys)

#### Treatment

- **First line: prednisone** (0.5–1 mg/kg per day, or higher if systemic involvement)
  - Adjunct: NSAIDs, colchicine and dapsone for fever, auricular chondritis, and arthralgias
- Immunosuppressive agents have variable response (MTX most effective)

#### Prognosis/clinical course

- In the past was a/w high morbidity and mortality
- Currently, w/ treatment, survival rates are >95% at 8 years
- **Chronic course w/ acute flares** lasting days to weeks → destruction of cartilage and collapse of supported structures
- **Most common causes of death = infection #1 (pneumonia)** > systemic vasculitis > large artery aneurysm dissection or rupture, airway collapse, renal failure, and malignancy
- Poor prognostic factors: anemia, saddle-nose deformity, arthritis, and vasculitis

### Mixed connective tissue disease

#### Epidemiology

- Strong female predominance (9:1)
- Majority present in second to fourth decades

#### Pathogenesis

- CTD characterized by overlapping features of ≥ two of the following: SLE, PM/DM, scleroderma, or RA
- Anti-U1RNP (high titers) antibodies thought to play pathogenic role
- a/w **HLA-DR4**

#### Clinical

- Three classification criteria for MCTD have been published, but **no current consensus**
- **Most common constellation:** Raynaud's, esophageal dysfunction, swollen fingers/hands ("sausage digits"), arthralgias/arthritis, and inflammatory myopathy

- Clinical findings
  - **Scleroderma-like findings:**
    - Raynaud's phenomenon (~100%): earliest and most common sign; can develop digital infarcts and gangrene
    - Esophageal dysmotility (85%)
    - Edema of hands, sausage digits
    - Sclerodactyly
    - Periungual telangiectasias w/ dropout areas
    - Pulmonary HTN (25%) = most serious complication of MCTD → accounts for 40% of MCTD deaths
    - Pulmonary fibrosis (usually mild)
    - Notably, do NOT see diffuse sclerodermoid involvement of face, trunk, and proximal extremities
  - **DM-like findings:**
    - Inflammatory myopathy +/- poikilodermatous areas on upper trunk and proximal extremities
    - Do NOT usually see DM-specific signs (Gottron's papules, heliotrope, psoriasiform scalp dermatitis)
  - **Lupus-like findings:** DLE, SCLE, or ACLE-like skin lesions
  - Other findings: **arthralgias/arthritis** (50%–70%), serositis (pleuritis and pericarditis), neurologic findings, cytopenias, APLS, and glomerulonephritis

#### Histopathology

- Varies depending on type of skin lesion biopsied

#### Laboratory testing

- (+) ANA with **speckled nuclear pattern**
- **High titer anti-U1RNP autoantibodies** (serologic hallmark)
  - Lacks anti-dsDNA, Smith antibodies, and hypocomplementemia → helps differentiate from SLE
- Cytopenias
- Antiphospholipid autoantibodies

#### Treatment

- First line: prednisone
- Adjuncts: NSAIDs, antimalarials
  - Lupus, RA, and DM-like features are more likely to be steroid-responsive compared with scleroderma-like features (e.g., sclerodactyly, Raynaud's, and pulmonary HTN)
- MTX is first line for severe arthritis, but should be used with caution due to **frequent pulmonary fibrosis in MCTD patients**

#### Prognosis/clinical course

- Good response to corticosteroid therapy and favorable prognosis
- 40% evolve into one of the six diffuse CTDs
  - Presence of **anti-dsDNA** → a/w evolution into **SLE**
  - Presence of esophageal hypomotility/dilation or sclerodactyly → a/w evolution into systemic sclerosis
- Survival rates
  - 5 year survival: 98%; 10 year survival: 88%
  - Mortality is due to: **pulmonary artery HTN (40%)** > acute cardiovascular events, TTP/HUS > infections



## Rheumatoid arthritis

### Epidemiology

- 1%–3% US adult population
- Female predominance (F:M = 3:1)
- Peak onset between 30–55 yo
- a/w HLA-DR1 and DR4

### Pathogenesis

- Self-reactive CD4+ T-cells produce Th1 and Th17 cytokines → promotes inflammation, stimulates synovial macrophages and fibroblasts to produce proinflammatory cytokines (e.g., TNF- $\alpha$ , IL-1, and IL-6) and proteases that break down cartilage and activate B-cells to differentiate into plasma cells → downstream effects:
  - RANKL (expressed by stromal cells, synovial fibroblasts, and T-cells) binds RANK on osteoclasts → **bone erosion**
  - RF and anti-CCP antibodies form immune complexes inside joints → activates complement cascade
- Majority of **cutaneous findings are due to neutrophil-mediated damage** (as a result of complement activation)
- Genetics:
  - PTPN22 gene
    - Encodes a lymphoid-specific protein tyrosine phosphatase, in which a gain of function polymorphism results in selection of autoreactive T-cells and B-cells (confers susceptibility to RA, JIA, and other CTDs)
  - HLA-DRB1
    - ↑propensity to develop autoantibodies against cyclic citrullinated proteins (CCP)
      - ◆ CCPs are proteins located within skin and joints!

### Clinical

- 2010 ACR/EULAR diagnostic criteria: requires score  $\geq 6$  points (out of 10 total possible points) for definite diagnosis
  - **Joint involvement:** swollen or tender joint, which may be confirmed by imaging ("large joints" = shoulders, elbows, hips, knees, and ankles; "small joints" = MCP, PIP, second to fifth MTP, thumb IP, and wrists joints with exclusion of DIP, first MTP, and first carpometacarpal joints)
    - One large joint (0 points)
    - 2–10 large joints (1 point)
    - 1–3 small joints (with or without involvement of large joints) (2 points)
    - 4–10 small joints (with or without involvement of large joints) (3 points)
    - More than 10 joints (at least one small joint) (5 points)
  - **Serology:**
    - Negative RF and negative CCP (0 points)
    - Low positive RF ( $\leq$  three times upper limit of normal) or low positive anti-CCP antibody ( $\leq$  three times upper limit of normal) (2 points)
    - High positive RF ( $>$  three times upper limit of normal) or high positive anti-CCP antibody ( $>$  three times upper limit of normal) (3 points)

- **Acute phase reactants:**
  - Normal CRP and normal ESR (0 points)
  - Abnormal CRP or abnormal ESR (1 point)
- **Duration of symptoms**
  - Shorter than 6 weeks (0 points)
  - $\geq 6$  weeks (1 point)
- Skin findings:
  - **Rheumatoid nodules (20%–30%)**
    - Usually occurs in patients w/ **high titer RF**
    - Firm, non-tender papules or nodules **over bony prominences** (esp. extensor forearm, dorsal hands and elbow), but can occur anywhere including visceral organs (Fig. 3-45)
    - Nodules located in dermis, subcutaneous tissue, or attached to periarticular capsule or tendons → may lead to tendon rupture
    - **Rheumatoid nodulosis:** disease variant where pts p/w multiple ulcerative nodules and **high RF, but in absence of active joint disease**
    - **Therapy-induced rheumatoid nodulosis**
      - ◆ Occurs in patients w/ preexisting RA, classically **following initiation of MTX** (termed MTX-induced accelerated nodulosis = "MAIN")
        - More recently described following initiation of TNF- $\alpha$  inhibitors
      - ◆ p/w **acute onset** of numerous symmetrically-grouped rheumatoid nodules; often **painful** (unlike normal rheumatoid nodules)
      - ◆ Typical locations: fingers, helix of ears, soles of feet, penis, chest, and surgical incision sites
  - **Rheumatoid vasculitis**
    - Late complication arising in pts w/ **history of severe erosive RA** (but joint disease is now burnt-out), **high titer RF** and rheumatoid nodules
    - CSVV or PAN-like eruption w/ **systemic vasculitis** (neuropathies, alveolitis, carditis, and cerebral infarction)
    - a/w **high mortality (up to 40%)** → must refer to **rheumatology for aggressive treatment** (cyclophosphamide + systemic steroids)



**Figure 3-45.** Rheumatoid nodules. Large rheumatoid nodules are seen in a classic location along the extensor surface of the forearm and in the olecranon bursa. (From Goldmann L, Schafer AI. Goldman-Cecil Medicine, 25th ed. Elsevier 2015)

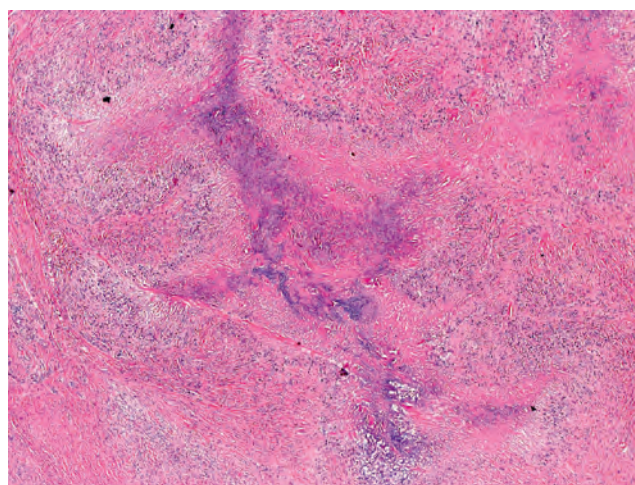
- Bywater's lesions
  - Purpuric papules usually on digital pulp; demonstrates LCV histologically
  - Not a/w systemic vasculitis of other organs (vs rheumatoid vasculitis)
- Superficial ulcerating necrobiosis (aka rheumatoid necrobiosis)
  - Atrophic, shiny, telangiectatic, yellow plaques w/ red-brown edges resembling NLD w/ ulceration
  - Typically numerous lesions on **bilateral lower extremities**
  - Occurs in patients with **severe RA w/ high titer RF** and rheumatoid nodules
- Neutrophilic dermatoses
  - Erythema elevatum diutinum
  - Sweet's syndrome
  - Pyoderma gangrenosum
  - **Rheumatoid neutrophilic dermatitis/dermatosis**
    - ◆ Persistent urticarial red papules/plaques symmetrically distributed on extensor forearms and hands
    - ◆ Histology: neutrophilic urticaria (or occasionally Sweet's-like)
  - MTX-induced papular eruption
    - ◆ Erythematous urticarial papules and plaques on buttocks and proximal extremities
    - ◆ Arise during treatment of disease flares w/ MTX
  - PNGD
    - ◆ Symmetrically distributed eroded, umbilicated papules overlying joints (elbows, knees, and knuckles)
    - ◆ May represent earliest phases of rheumatoid nodules
  - IGDA
    - ◆ Annular red-violaceous plaques on trunk and intertriginous areas, sometimes with "**rope sign**" (red-flesh colored cords extending down flanks or back)

### Histopathology

- Rheumatoid nodules
  - Early lesions (resembles PNGD and IGDA): interstitial granulomatous or neutrophilic infiltrate +/- LCV
  - Later (well-developed lesions): **large palisading granulomas** surrounding degenerated **eosinophilic connective tissue ("necrobiosis")** and **fibrin** in deep dermis or subcutaneous tissue, often w/ neutrophilic debris
- Rheumatoid vasculitis: histologic features correlate w/ clinical morphology → may see palpable purpura or PAN-like changes
  - DIF: strong IgM and C3 in small and medium sized vessels (vs weaker and limited to medium sized vessels in classic PAN)

### Laboratory findings

- (+) RF (sensitivity 80%, specificity 85%)
- Anti-CCP (sensitivity 70%, specificity 95%)



**Figure 3-46.** Rheumatoid nodule – histologic features. A large irregular area of necrobiosis surrounded by a palisade of histiocytes. Courtesy, Lorenzo Cerroni, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

### Treatment

- Arthritis management
  - Goal of therapy: decrease disease activity to control symptoms and prevent end-organ damage
  - **Glucocorticoids**: used for rapid disease control before onset of efficacy of DMARDs
  - Disease-modifying anti-rheumatic drugs (DMARDs)
    - Non-biologic DMARDs (first line)
      - ◆ MTX, sulfasalazine, hydroxychloroquine, and leflunomide
    - Biologic DMARDs (second line)
      - ◆ TNF- $\alpha$  inhibitors, abatecept, tocilizumab (IL-6R inhibitor), and rituximab
  - NSAIDs used as adjunct to DMARDs
- Rheumatoid nodules
  - **Do not respond to treatment for arthritis** → consider intralesional corticosteroids ( $\downarrow$ size) or excision (but recurrences common)

### Prognosis/clinical course

- Majority have chronic progressive disease activity that waxes and wanes over time
- A few patients may exhibit an aggressive form of rapidly progressive and erosive arthritis
- Mortality rate two times higher than general population → most common causes of death = ischemic heart disease (most common) and infection
- Poor prognostic factors: extraarticular disease, low functional capacity, low socioeconomic status, low education, and chronic prednisone use

### Additional boards factoids

- **Felty syndrome**: seropositive RA characterized by neutropenia, splenomegaly, and refractory leg ulcers (may resemble PG)
  - a/w  $\uparrow$  risk of lymphomas/leukemias
  - Rx: G-CSF and/or **splenectomy**

## Systemic-onset juvenile idiopathic arthritis (Still's disease)

### Epidemiology

- Still's disease is just one of many forms of JIA (20% of all JIA), but is more relevant to Dermatologists because **other forms of JIA rarely have skin findings**
  - Other forms of JIA (will not be discussed further):
    - RF(-) Polyarthritis (5%)**: Favors small joints (hands and feet); usually non-erosive; RF(-) and ANA(-)
    - RF(+) Polyarthritis (15%)**: Favors small joints (hands and feet); usually erosive; shares same features as adult RA → **Rheumatoid nodules**, RF(+) in 100%, usually ANA(+)
    - Oligo/pauciarticular arthritis (60%)**: Most common form of JIA; favors knees; divided into two types → Type I (most common subtype; onset = 1-8yo; uveitis in 50%; ANA(+), RF-negative); Type II (onset = 9-16 yo; strongly a/w HLA-B27; RF(-), ANA-negative)
    - Other rare forms: Enthesitis-related arthritis (a/w HLA-B27), PsA (ANA-negative, a/w anterior uveitis)
- JIA is the **most common rheumatologic disease in childhood**
- M = F (in contrast, all other forms of JIA have female predominance)
- By definition, onset ≤ 16 yo (mean age = 6 yo)

### Pathogenesis

- Best classified as an **autoinflammatory syndrome** (disorder of innate immune system), rather than autoimmune disease (disorder of adaptive immune system)
  - Activation of innate immune system → ↑IL-1 production by the inflammasome → downstream effects
    - Recent (2014) study demonstrated up to 3-fold increased risk of JIA in kids exposed to multiple courses of antibiotics

### Clinical

- Diagnostic criteria:
  - High episodic fevers** (>38.9°C) daily for ≥ 2 weeks and documented to be quotidian for ≥ 3 days
    - Classically arises in late afternoon to early evening
  - Plus one of the following features:
    - Transient evanescent, salmon pink, blanching eruption** (90%): typically arises in late afternoon/evening (**corresponds w/ fever spikes**); p/w generalized distribution (favors axilla and waist); **Koebnerization** w/ linear lesions (**Fig. 3-47**)
      - Less common skin findings: **persistent papules and plaques**, periorbital edema, rheumatoid nodule-like lesions
    - Generalized lymphadenopathy
    - Hepatomegaly/splenomegaly
    - Serositis (pericarditis, pleuritis, and peritonitis)
    - Symmetric polyarthritis > oligoarthritis; erosive in 20%



**Figure 3-47.** Evanescent eruption of Still's disease. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

### Histopathology

- Two types of cutaneous lesions, each w/ distinctive features:
  - Evanescent transient exanthem**: edema of superficial dermis, superficial, perivascular, and interstitial **neutrophilic infiltrate** (denser and more neutrophil-predominant than urticaria) in **absence of vasculitis**
  - Persistent papules/plaques**: same as above + **parakeratosis, superficially-scattered necrotic keratinocytes**

### Laboratory testing

- Leukocytosis, anemia, and thrombocytosis
- ↑ESR/CRP
- ↑↑↑Ferritin (extremely high)
- RF-negative (>95%)
- ANA-negative (>95%)

### Treatment

- Mild articular or extra-articular disease: **NSAIDs** +/- Hydroxychloroquine
- Moderate or severe disease: **Systemic steroids** +/- steroid-sparing immunosuppressants (MTX, TNF-α inhibitors)
- IL-1 receptor** (e.g., **anakinra**, rilonacept, canakinumab) and **IL-6 receptor** (e.g., tocilizumab) antagonists have demonstrated **promising results** for Still's; may consider hematopoietic stem cell transplantation for refractory disease

### Prognosis/clinical course

- Arthritis resolves completely in 50%
  - Other 50% have a chronic course w/ persistent arthritis and systemic complications



- Extensive arthritis or symptoms lasting > 6 months → a/w poorer prognosis
- 5% develop macrophage activation syndrome (life-threatening)
  - Highly activated immunologic state → hemophagocytosis and cytokine overproduction
  - Characterized by pancytopenia, coagulopathy, hepatic dysfunction, and neurologic complications
  - Requires treatment w/ high dose systemic corticosteroids/other immunosuppressants

## Adult onset Still's disease

### Epidemiology

- Vast majority < 30 yo
- Slight female predominance

### Pathogenesis

- Possibly a reactive condition triggered by an infectious agents
- a/w numerous HLA groups, suggesting genetic element

### Clinical

- **Prodrome of flu-like illness w/ sore throat**, constitutional symptoms, **high fever**, arthralgias, and myalgias
- **Fever usually >39°C w/ spiking pattern** (late afternoon to early evening)
- Skin manifestations
  - **Salmon patch exanthema** (asymptomatic and transient)
    - Occurs concomitantly with fever spikes
    - Typical location: trunk and sites of pressure with Koebnerization
  - **Violaceous to reddish-brown, scaly, persistent papules and plaques** (50%)
- Systemic manifestations
  - Arthralgias/arthritis (65%–100%)
    - Typically involves knees, wrists, and ankles symmetrically
    - **Carpal ankylosis (characteristic feature)**: limited range of motion with minimal pain
  - Hepatosplenomegaly
- Complications
  - Macrophage activation syndrome (15%) → life-threatening!

### Histopathology

- Same as SoJIA (classic Still's disease)

### Laboratory findings

- Negative ANA and RF
- Anemia, leukocytosis and thrombocytosis common
- ↑ESR/CRP
- ↑↑↑ferritin
  - Levels correlate w/ disease activity
  - a/w chronic pattern of disease, recurrent flares, and poor prognosis
- Laboratory abnormalities a/w macrophage activation syndrome (MAS)

### Treatment

- Majority require **systemic steroids** (Prednisone 40–60mg/day)
  - May add steroid-sparing agent (MTX = first choice)
- Inhibitors of IL-1 receptor (anakinra), and IL-6 receptor (tocilizumab) may be beneficial

### Prognosis/clinical course

- Usually benign, non-fatal course, w/ low mortality (3%–10%)
- Deaths due to infections, ARDS, and multiple organ failure from MAS and thrombotic microangiopathy

## Morphea (localized scleroderma)

### Epidemiology

- Two thirds of cases present in childhood
- F > M (2.6:1)
  - Exception: linear morphea has no gender predilection
- Frequencies of various morphea types:
  - Plaque (>50%): **most common subtype in adults**
  - Linear (20%): **most common subtype in children**
  - Generalized (13%)
  - Morphea profunda (11%)

### Pathogenesis

- Genetic predisposition + environmental trigger → vascular injury (e.g., decreased capillary density, endothelial injury) → inflammation → profibrotic Th2 cytokines (IL-4, IL-6, and TGF-β) → fibroblast proliferation and collagen deposition
- Environmental triggers: trauma, radiation, medications (e.g., bleomycin, bromocriptine, and D-penicillamine), and *Borrelia* spp. (Europe and Japan mainly; a/w *Borrelia afzelii* and *B.garinii*)

### Clinical features

- Clinical subtypes
  - Plaque morphea (most common form overall, and in adults)
    - Begin as erythematous to violaceous patches on **trunk and proximal extremities** → evolve into indurated **hyperpigmented or ivory plaques**; plaques often **hairless and anhidrotic**, w/ prominent follicular orifices
    - May have surrounding **lilac-violaceous inflammatory rim** (indicates persistent activity) (Fig. 3-48)
    - Often develops in areas of pressure
  - Guttate morphea
    - Multiple, small chalk white, flat or slightly depressed macules; only minimally indurated
    - Appears similar to guttate LS&A but lacks follicular plugging and epidermal atrophy
    - Typical locations: upper half of trunk
  - Linear morphea
    - Important because a/w **significant morbidity** (esp. in kids)
    - Morphology similar to plaque morphea, but with **linear distribution**, often following Blaschko's lines



- Most common sites: **lower extremities (#1)** > upper extremities > head, trunk
- May involve deeper structures (muscle, fascia, and bone)
- **Anti-ssDNA** autoantibodies common
- Typical locations: extremities and trunk
- Complications: **undergrowth of limbs (permanent!)** (Fig. 3-49), deformity, joint

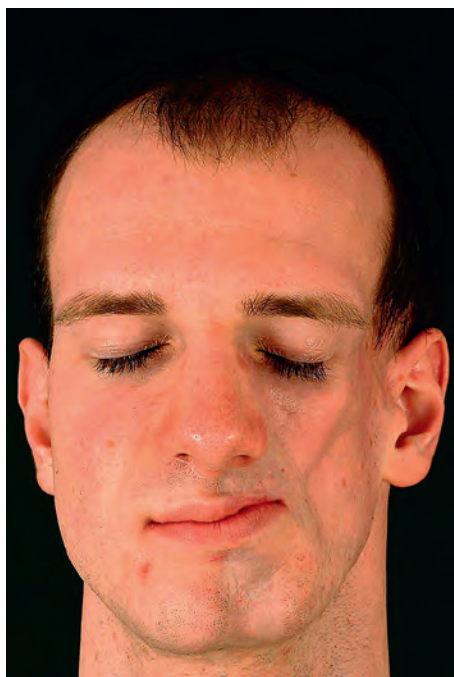


**Figure 3-48.** Morphea. A single or few oval areas of non-pitting erythema and edema typically appear on the trunk. A violaceous border (lilac ring) surrounds the indurated area. The center of the lesion then develops smooth, ivory-colored hairless or hyperpigmented plaques, and the ability to sweat is lost. (From Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 6e. Elsevier 2015)

- restriction/contractures (risk highest if plaques extend over joints), and arthralgias
- Head/neck subtypes of linear morphea:
  - ◆ **En coup de sabre:**
    - Indented appearance of frontal, frontoparietal, or parasagittal forehead or scalp
  - ◆ **Parry-Romberg syndrome** (aka progressive hemifacial atrophy)
    - Unilateral atrophy of face involving dermis, subcutaneous tissue, muscle, and bone (Fig. 3-50 and Fig. 3-51)
    - May have associated epilepsy, exophthalmos, headache, trigeminal neuralgia, myopathy of the eye muscles, cerebral atrophy, white matter hyperintensity, or alopecia
  - ◆ Children with head/neck morphea should have regular ophthalmologic examinations to monitor for asymptomatic ocular involvement
- **Atrophoderma of Pasini and Pierini**
  - Large (up to 20 cm) brownish-gray hyperpigmented oval, atrophic, well-demarcated plaques w/ **sharp sloping borders (“cliff drop”)**
  - Typical location: trunk/upper arms of young females (typically second to third decades)
  - Begins as a persistent single lesion with additional lesions forming over time
  - Histology: ↓↓**dermal thickness** compared to normal skin
    - ◆ Biopsy should contain affected skin and adjacent normal skin to show “cliff drop”



**Figure 3-49.** Linear morphea of the leg in two adolescents. **(A)** Extensive induration of the left leg with hypoplasia and an obvious flexion contracture of the knee; there is also involvement of the right foot. **(B)** Linear distribution of coalescing sclerotic plaques on the thigh; note the lilac-colored border. Part (B) is courtesy, Julie V Schaffer, MD. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)



**Figure 3-50.** Marked atrophy of subcutaneous structures, including bone. (Courtesy of Sommer A et al. J Amer Acad Dermatol. 2006;54(2):227–233)



**Figure 3-51.** Hemiatrophy of the tongue. (Courtesy of Sommer A, et al. J Amer Acad Dermatol 2006;54(2):227–233)

○ Variant:

- ◆ **Linear atrophoderma of Moulin:** linear form of atrophoderma that is chronic but non-progressive with benign course; less induration and pigmentary changes compared with other types of morphea

- Generalized morphea
  - Widespread indurated plaques that expand to involve entire trunk and extremities → **muscle atrophy and difficulty breathing** (due to constrictive effect of taut skin on chest)
  - Most likely form to have extracutaneous symptoms (fatigue, malaise, and myalgias/artralgias)
  - Spontaneous resolution uncommon
  - Usually (+)ANA
  - Variant:
    - ◆ Pansclerotic morphea:
      - Children <14 yo
      - Type of generalized morphea involving deep structures → disability and contractures of extremities
- Bullous morphea
  - Rare, usually only seen in context of generalized morphea
  - Etiology: diffuse sclerosis of skin → impaired lymphatic flow → formation of lymphoceles/bullae
- Deep morphea (morphea profunda)
  - Morphea primarily involving subcutaneous tissue (fascia, muscle, and bone) w/ deep induration; overlying skin can appear normal, puckered (“pseudo-cellulite”), or hyperpigmented
  - Poor response to corticosteroids (vs eosinophilic fasciitis)
  - Can develop osteoma cutis in lesions
  - Complications: deformity, ulcers, SCC formation, joint restriction, and contractures
- Nodular morphea (keloidal morphea)
  - Hyperpigmented sclerotic nodules that mimic keloids; can be a/w classic plaque morphea
- Morphea-lichen sclerosis overlap
  - Patients w/ combination of morphea and LS&A lesions

### Histopathology

- Early
  - Lymphocytic infiltrate w/ plasma cells at dermal-SQ junction
  - Loss of CD34+ dendritic cells (vs ↑ in NSF and scleromyxedema)
- Later
  - Decreased inflammation
  - “Square-biopsy” sign
  - Pale, edematous, and homogenized papillary dermis
  - Loss of pilosebaceous units/periadnexal fat
  - “Trapped eccrine glands” = eccrine glands/ducts compressed by surrounding sclerotic collagen

### Laboratory testing

- All forms of morphea **lack anti-Scl70 (Topo I) and anti-centromere antibodies!** (in contrast to SSc)
- All forms have **(+) anti-topoisomerase II antibodies** (75% overall, 85%–90% in generalized morphea)
- Plaque morphea:
  - Usually (–)ANA
  - Lacks anti-ssDNA and anti-histone antibodies

- Linear and generalized morphea:
  - More likely to be (+)ANA than other forms
  - Often (+) anti-ssDNA and (+) anti-histone antibodies  
→ correlates w/ disease severity/activity
- ESR/CRP may be ↑, especially in linear or deep morphea

### Treatment

- See treatment algorithm (Fig. 3-52)
- Treatment can halt disease progression
- Topical therapies used for superficial circumscribed lesions
  - Topical or intralesional corticosteroids can be used, but may cause atrophy
  - TCIs, vitamin D analogues, and imiquimod all have reported efficacy
- UVA1 phototherapy considered for more extensive disease, but can only penetrate the dermis so no benefit for deeper lesions
- ToC for moderate to severe morphea is MTX, often in combination with systemic corticosteroids for the first 2 to 3 months

### Prognosis/clinical course

- Superficial plaque morphea often self-limited; softens over 3–5 years
- Generalized morphea has worse prognosis
- Important to treat childhood linear morphea aggressively  
→ prevents limb shortening and joint contractures

### Additional boards factoids

- Melorheostosis = roughening long bone surfaces underlying area of linear morphea (also Buschke-Ollendorff syndrome) that resembles wax dripping down the side of a candle on X-ray

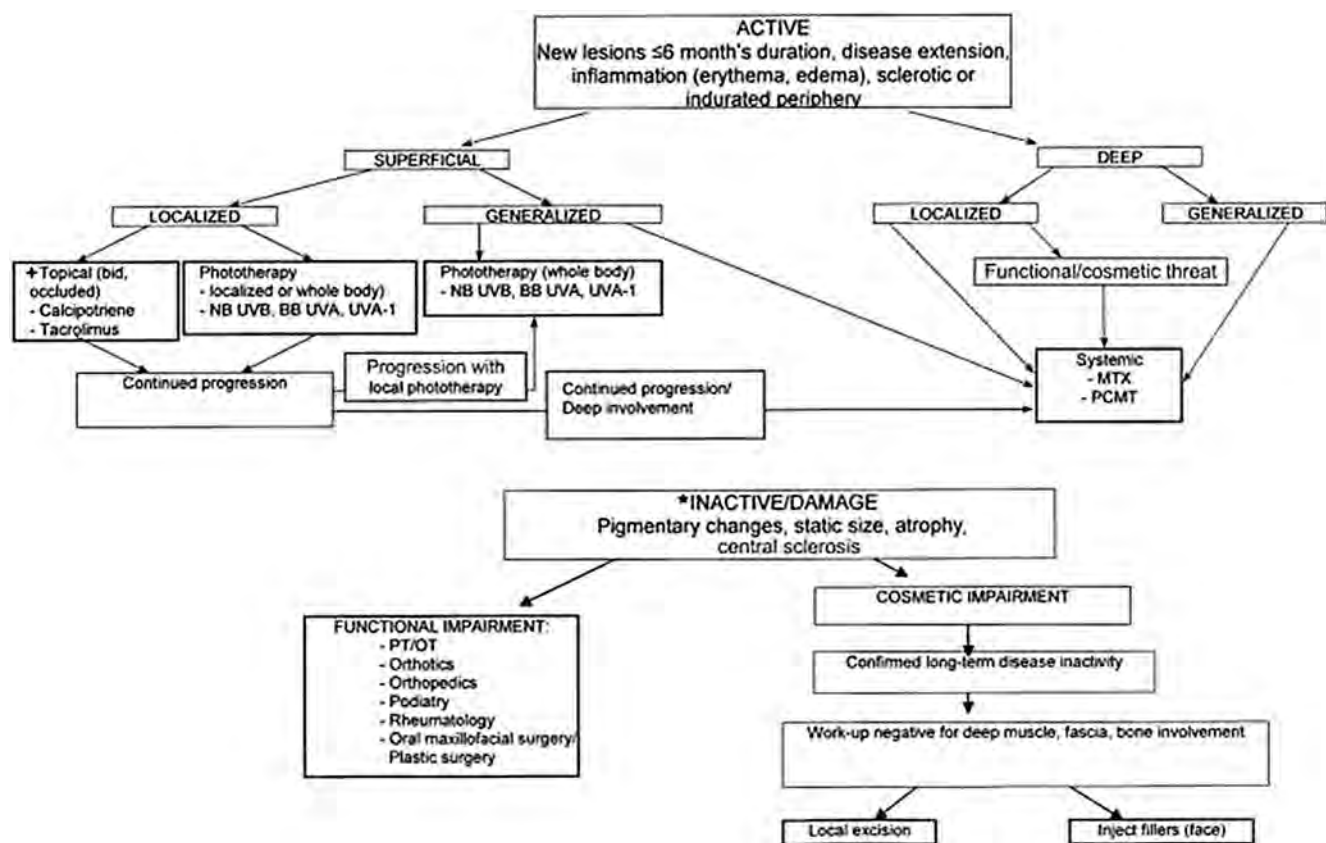
## Scleroderma (aka systemic sclerosis)

### Epidemiology

- F > M (3:1)
- Typical age of onset: 30–50 yo

### Pathogenesis

- Key pathogenic features include vascular dysfunction, cellular and humoral immune dysregulation, and excess



**Figure 3-52.** Therapeutic algorithm for morphea based on existing evidence. Superficial involvement is defined by histologic evidence of papillary dermal involvement. Deep involvement is defined as sclerosis or inflammation of reticular dermis, subcutis, fascia, or muscle. Histologic examination and/or magnetic resonance imaging are encouraged to evaluate lesions for depth of involvement and, likewise, determine appropriate treatment and evaluation of therapeutic efficacy. BB (Broadband); MTX (methotrexate); NB (narrowband); PCMT (pulsed intravenous corticosteroids plus methotrexate); PT (physical therapy); OT (occupational therapy); UV (ultraviolet). \*There is very little evidence for any therapy addressing disease damage in morphea. There is minimal evidence for efficacy of these measures. Risk of disease reactivation is also unknown, but surgical measures should only be undertaken in long-standing, inactive disease. Topical therapies should not be used as monotherapy in the presence of active and progressively functional impairment (e.g., decreased range of motion, contracture, and limb length discrepancy). Systemic manifestations most commonly reported to occur in morphea include arthritis, seizures/headaches (en coupe de sabre), and ocular manifestations. All patients with morphea should be assessed for their presence and appropriate referrals made. (Courtesy of Zwischenberger BA et al. J Am Acad Dermatol 2011;65:925–941)



collagen/ECM protein deposition in skin and internal organs

- **Vascular dysfunction**, primarily of microcirculation, is the earliest feature and consists of endothelial injury with vascular leakage, abnormal vasospasms, intimal proliferation, luminal obstruction, capillary destruction and devascularization
- **Autoantibody production** (e.g., **anti-centromere** and **anti-Scl70**), auto-antigen driven T-cell activation with a Th2-predominant profile and **↑production of profibrotic cytokines/growth factors** (IL-2, IL-13, TGF- $\beta$ , PDGF, and endothelin-1) → accumulation of myofibroblasts in affected tissues → excess collagen production (predominately types I and III) and other ECM proteins

### Clinical features

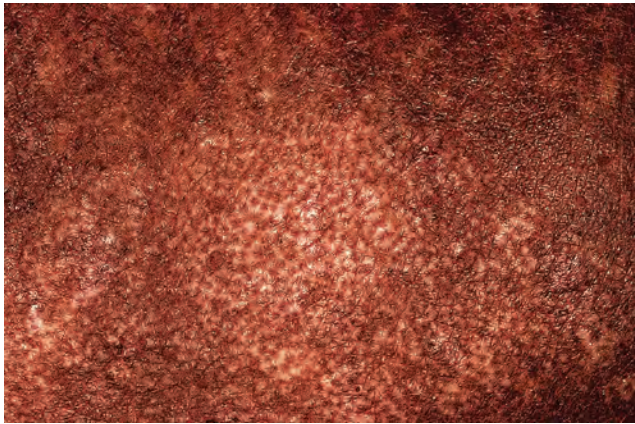
- Diagnostic criteria: score  $\geq 9$  classified as definite SSc (sensitivity 91%; specificity 92%)
  - Skin thickening of fingers of both hands extending proximal to MCP joints (9 points, sufficient criterion)
    - Early (edematous) phase (Fig. 3-53): pitting edema of digits
      - ◆ Initial presenting sign in 50%
    - Indurated phase: edematous fingers harden and become tight and shiny
    - Late (atrophic) phase: skin atrophy with flexion contractures
  - Skin thickening of fingers (only count higher score)
    - Puffy fingers with diffuse, non-pitting increase in soft tissue (2 points)
    - **Sclerodactyly** of the fingers (distal to the four MCP joints, but proximal to the PIP joints) (4 points)
  - Fingertip lesions with loss of substance from finger pad (only count higher score)
    - Digital tip ulcers (2 points)
      - ◆ Thought to be due to trauma



**Figure 3-53.** Early edematous phase of systemic sclerosis. Note the demonstration of pitting edema on two of the digits. Courtesy, Jean L. Bolognia, MD. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- Fingertip pitting scars (3 points)
  - ◆ Thought to be due to ischemia
- Telangiectasia (2 points)
  - **Matted telangiectasias** of face/lips/palms (more common in limited SSc/CREST):
    - ◆ Telangiectasias have smooth/"mat-like" squared-off edges
    - ◆ In contrast, hereditary hemorrhagic telangiectasia (HHT, Osler Weber Rendu) has irregular telangiectasias w/ radiating vessels
- Abnormal nail fold capillaries (2 points)
  - **Dilated capillary loops alternating w/ capillary drop out**
- Pulmonary arterial hypertension (PAH) and/or interstitial lung disease (ILD) (maximum score is 2)
  - PAH (2 points)
  - ILD (2 points)
- Raynaud's phenomenon (3 points)
  - Leading cause of secondary Raynaud's phenomenon
  - Initial presenting sign in 50% of SSc
- Any SSc-related autoantibodies: anti-centromere, anti-topoisomerase I (Scl-70), or anti-RNA polymerase III) (3 points)
- SSc subtypes:
  - Limited systemic sclerosis (SSc)
    - Definition: limited involvement of **distal extremities** (distal to MCP/MTP joints) and **face**
    - **Lacks severe renal/pulmonary involvement** → improved overall mortality
      - ◆ Commonly see isolated pulmonary artery hypertension
    - Variants:
      - ◆ **CREST syndrome**
        - Calcinosis cutis (40%)
        - Raynaud's phenomenon (99%)
        - Esophageal dysmotility (90%)
        - Sclerodactyly
        - Telangiectasias (mat telangiectasias; 90%)
      - ◆ Systemic sclerosis sine scleroderma:
        - Raynaud's phenomenon and positive serology, but no cutaneous involvement
  - Diffuse systemic sclerosis ("progressive systemic fibrosis," PSS)
    - a/w more **severe visceral disease** and worse prognosis
    - Sclerosis involving **distal and proximal extremities** as well as the **face and trunk**
- Other cutaneous findings
  - **Beaked nose, microstomia**, and loss of wrinkles
  - Calcinosis cutis, usually over joints, may ulcerate
  - Xerotic itchy skin
  - Dyspigmentation: two types
    - Diffuse hyperpigmentation in sun-exposed or pressure related areas
    - Hypopigmentation of upper trunk/face with perifollicular sparing ("**salt and pepper**" sign) (Fig. 3-54)





**Figure 3-54.** The “salt and pepper” sign. Leukoderma with retention of perifollicular pigmentation in a patient with systemic sclerosis. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- **Pterygium inversum unguis:** extension of hyponychium on undersurface of nail plate
- Extracutaneous findings ranging from asymptomatic to severe
  - Pulmonary (70%)
    - **Most common cause of mortality**
    - ILD (more common in diffuse SSc/PSS)
    - Pulmonary hypertension (more common in limited SSc/CREST)
  - Cardiovascular
    - ↑risk of atherosclerosis, MI, and stroke
    - Myocardial fibrosis → **restrictive cardiomyopathy** and arrhythmias
  - GI (90%)
    - **Most common site of visceral disease**
    - a/w **morbidity but no ↑risk of mortality**
    - Lower esophageal dysphagia/dysmotility (90%) → aspiration and esophagitis
    - Gastroparesis
    - Gastric antral vascular ectasia (GAVE, aka watermelon stomach) (1%–20%)
    - Small and large bowel dysmotility
    - Weak rectal tone → stool incontinence
  - Renal
    - Scleroderma renal crisis (SRC)
      - ◆ p/w rapid rise in creatinine
      - ◆ Affects 20% of **diffuse SSc** patients (PSS)
      - ◆ Almost never seen in limited SSc
      - ◆ **ACE-I will decrease risk**
  - MSK
    - Arthralgias/arthritis
    - Palpable tendon friction rubs

#### Histopathology

- Same as morphea

#### Laboratory testing

- (+)ANA (>90%)
- Anti-centromere
  - a/w **limited SSc** > diffuse SSc
  - ↑risk of PAH and digital ulcers

- Anti-topoisomerase I (anti-Scl-70)
  - a/w **diffuse SSc** > limited SSc
  - ↑risk of ILD, digital ulcers, synovitis, joint contractures, and cardiac involvement
- Others: [Table 3-11](#)

#### Treatment

- **Most important goal = control internal organ involvement!**
  - Renal disease: **ACE inhibitors** prevent SRC
  - Pulmonary disease:
    - ILD: cyclophosphamide, rituximab, MMF, HSCT, and adjuvant N-acetylcysteine
    - PAH: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostanoids
  - GI involvement: PPIs for GERD symptoms and promotility agents
  - Cardiac involvement: anti-hypertensives, MMF, and cyclophosphamide
- Specific skin-directed treatments (often ineffective):
  - Raynaud's phenomenon: tobacco cessation, cold temperature avoidance, and vasodilators (CCBs, phosphodiesterase type 5 inhibitors, topical nitroglycerin, prostanoids, and endothelin receptor antagonists)
  - Digital ulcers: first line = same measures as per Raynaud's; other options include IV iloprost (prostacyclin analogue; proven efficacy in RCT) and Bosentan (endothelin receptor antagonist; efficacy in RCT preventing new ulcers)
  - Cutaneous sclerosis: phototherapy (PUVA, UVA1), extracorporeal photophoresis, glucocorticoids, immunosuppressives (MMF and rituximab), and autologous HSCT (has shown efficacy in RCT)
  - Calcinosis cutis: **surgical excision** (can recur), CCBs (questionable efficacy), and extracorporeal shock-wave lithotripsy

#### Prognosis/clinical course

- Mortality (10 year survival):
  - Diffuse SSc (PSS): 50%
  - Limited SSc: 70%
- Due to the use of ACE-inhibitors for SRC, **ILD is now the #1 cause of death**
  - Screen for lung disease w/ **high-resolution CT and PFTs**
- Indicators of poor survival
  - Older age, male, African Americans, poor socioeconomic status
  - ↑ ESR and anemia
  - Major organ involvement: myositis, extensive cutaneous disease, heart involvement, ILD, and PAH
  - Presence of palpable tendon friction rubs

#### Additional boards factoids

- Raynaud's and hand edema are the two earliest and most common presenting features of SSc
- CXCL4 is a new biomarker for skin and lung fibrosis and PAH

## Eosinophilic fasciitis (Shulman syndrome)

### Epidemiology

- Female and Caucasian predominance
- Most present in fourth to sixth decades

### Pathogenesis

- Pathogenesis unknown, but TGF- $\beta$  levels markedly elevated
- a/w recent history of strenuous activity (30%)
  - Other potential triggers: trauma, borreliosis, and statin use

### Clinical features

- Key feature = **rapid onset of symmetric edema/induration** and pain in extremities in a/w **peripheral eosinophilia**
  - Spares hands, feet, and face
  - Progresses to woody induration and fibrosis with a **peau d'orange** ("pseudo-cellulite" appearance)
  - "Dry river bed" or "groove sign" = linear depressions of veins within indurated skin
  - **Lacks Raynaud's** phenomenon
- Disease associations (not very common): inflammatory arthritis, joint contractures, carpal tunnel syndrome, hemolytic anemia, myelodysplastic disorder, lymphoma/leukemia, MGUS, and multiple myeloma
- DDx:
  - SSc:
    - EF spares hands, feet, and face
    - EF lacks Raynaud's and visceral involvement
  - Eosinophilia-myalgia syndrome (L-tryptophan), Spanish toxic oil syndrome (rapeseed oil)
    - EF lacks prominent systemic symptoms (fever, myalgias, and pulmonary involvement)

### Histopathology

- **Massive thickening and fibrosis of deep fascia** (10 to 50 times the normal width); lymphoplasmacytic infiltrate +/- eosinophils
  - Must obtain deep biopsy (to fascia)
  - Eosinophils occasionally present in biopsy, however, **tissue eosinophilia is NOT essential to diagnosis** → **peripheral eosinophilia is more typical!**

### Laboratory testing

- **Peripheral eosinophilia (80%)**, ↑ESR, hypergammaglobulinemia
- Metalloproteinase inhibitor-1 (TIMP-1) = new serologic marker of disease activity
- MRI or CT scan demonstrates fascial thickening → may eliminate need for biopsy in some cases

### Treatment

- **Excellent response to systemic steroids** (vs deep morphea)
- Steroid sparing agents: hydroxychloroquine, cyclosporine, dapsone, MTX, PUVA, UVA1 +/- acitretin, and TNF- $\alpha$  inhibitors
- **Physical therapy** to prevent joint contractures

### Prognosis/clinical course

- Up to one third may resolve spontaneously, but some degree of induration usually persists
- Response to steroids can be appreciated after a few weeks
- Features a/w refractory disease:
  - Concomitant morphea-like skin lesions
  - Truncal involvement
  - Younger age of onset
  - Dermal fibrosis on histopathology

## Nephrogenic systemic fibrosis (nephrogenic fibrosing dermatopathy, NSF/NFD)

### Epidemiology

- Typically presents in fifth decade
- No gender or race predilection

### Pathogenesis

- Fibrosis of skin and internal organs occurs as a result of **gadolinium-containing contrast exposure** in the setting of **acute kidney injury or severe CKD**
  - Theory: gadolinium leaks into tissues → engulfed by macrophages → release profibrotic cytokines and growth factors → "**circulating fibrocytes**" (CD34+, **ProCollagen I+** cells) recruited to skin → excess collagen and ECM production
- Onset: typically **2 to 4 weeks after gadolinium exposure**, but can occur after several years

### Clinical features

- Cutaneous findings
  - Insidious onset of symmetrically distributed, painless, **hyperpigmented and indurated "patterned plaques"** (reticular or polygonal morphology) (Fig. 3-55)
    - **Extremities > trunk**
  - Deep induration of proximal extremities resulting in a "pseudocellulite" or cobbled appearance
  - Marked **woody induration** with peau d'orange changes
  - Puckering or **linear banding** due to focal areas of bound-down skin on proximal extremities
  - Dermal papules: brawny to skin-colored papules or nodules with absent epidermal change
- **Scleral plaque** (exam favorite!): white-yellow plaques w/ dilated capillaries in patients <45 yo (above this age, scleral plaques are less specific because of the clinical overlap w/ pinguecula) (Fig. 3-56)
- Extracutaneous involvement (very rare)
  - Fibrosis and calcification of rete testis, dura mater, diaphragm, renal tubules, heart, and lungs

### Histopathology

- Very similar to scleromyxedema, but fibrosis usually extends more deeply (into fat and fascia)
  - Diagnostic findings are most prominent in subQ fat septae → **must obtain deep biopsy (to fascia)**
  - ↑**collagen** (bundles only slightly thickened) increased **spindled fibrocytes** (CD34+ and procollagen1+) extending deeply into SQ fibrous septae



**Figure 3-55.** Hyperpigmented sclerotic plaques of nephrogenic fibrosing dermopathy. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)



**Figure 3-56.** Nephrogenic systemic fibrosis (NSF) – clinical features. Scleral plaques in a patient less than 45 years of age and is a minor criterion for NSF. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- In contrast, morphea and scleroderma have loss/decreased CD34+ cells in dermis
- ↑Mucin

#### Laboratory testing

- ↑Cr/BUN
- Calcium and/or phosphorus abnormalities

#### Treatment

- Refractory to treatment w/ corticosteroids and other immunosuppressives

- Treatment of kidney disease is most important → may slow or improve NSF
- Physical therapy for all pts to prevent joint contractures
- Anecdotal reports of improvement w/ imatinib, rapamycin, PDT, UVA-1, IVIG, plasmapheresis, extracorporeal photopheresis, and discontinuation of erythropoietin

#### Prognosis/clinical course

- Chronic, progressive course
- 2 year mortality rate: ~50%

#### Additional boards factoids

- Know the differences between the major sclerosing/fibrosing dermopathies (Table 3-14)

### Other sclerosing/fibrosing skin disorders (Table 3-15)

## ABNORMALITIES OF DERMAL FIBROUS AND ELASTIC TISSUE

### Perforating diseases (elastosis perforans serpiginosa, reactive perforating collagenosis/acquired perforating dermatosis, and perforating calcific elastosis)

- Discussed in Table 3-16
- All are characterized by transepidermal elimination of dermal connective tissue
- All p/w papules and nodules with keratotic plugs
- Treatment
  - EPS/RPC generally mild; treat w/ local therapies, avoid trauma
  - Acquired perforating dermatosis difficult to treat: broad or narrowband UVB most effective

### Abnormalities of connective tissue

- Discussed in Table 3-17

## 3.6 GRANULOMATOUS/HISTIOCYTIC DISORDERS

### Non-infectious granulomas

#### Granuloma annulare

##### Epidemiology

- Children and young adults most commonly affected (two-thirds arise before 30yo)
- F > M (2:1)

##### Pathogenesis

- Unknown etiology; most likely Th1-type delayed hypersensitivity reaction to a variety of triggers (trauma/

**Table 3-14.** Major Clinical and Laboratory Manifestations of Systemic Sclerosis and Other Selected Conditions Characterized by Cutaneous Induration

	Systemic Sclerosis	Morphea	Eosinophilic Fasciitis	Scleredema	Scleromyxedema	NSF
Major clinical variants	Limited Diffuse	Plaque-type morphea Linear morphea Generalized morphea		Post-infectious (type I) Monoclonal gammopathy-associated (type II) Diabetes mellitus-associated (type III)		
Raynaud's phenomenon	++	–	–	–	–	–
Symmetric induration	++*	–	++*	++	++	+
Sclerodactyly	++	–	–	–	–	–
Facial involvement	+	– plaque-type and generalized + linear (en coup de sabre)	–	± types I and II – type III	+	–
Systemic involvement	++	–	Uncommon	–	++	+
Antinuclear antibodies	++	± generalized and linear – plaque-type	–	–	–	–
Anti-centromere antibodies	+ limited SSc	–	–	–	–	–
Anti-topoisomerase I (Scl-70) antibodies	+ diffuse SSc	–	–	–	–	–
Monoclonal gammopathy	–	–		+ type II	++	–
Spontaneous remission	–	++ plaque-type + generalized ± linear	++	++ type I ± types II and III	–	±†

NSF, nephrogenic systemic fibrosis; ++, almost always; +, common; ±, sometimes; –, rare or unusual Courtesy, Vincent Falanga, MD  
 \*May be preceded by edematous phase.  
 †With improved renal function.  
 (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 3-15.** Other Sclerosing/Fibrosing Skin Disorders

Disease	Clinical	Other
<i>Mucinoses</i>		
Scleredema	Erythema and woody induration of skin with a <b>peau d'orange</b> appearance; visceral involvement rare <b>Type 1 (55%)</b> : usually preceded by URI, especially <b>Strep</b> pharyngitis; typically affects middle-aged women, involving the face (expressionless face w/open mouth), neck, trunk, proximal upper extremities; usually resolves after 6 mos–2 yrs <b>Type 2 (25%)</b> : same clinical presentation as type 1, but with associated <b>IgGκ</b> monoclonal gammopathy <b>Type 3 (20%, aka scleredema diabeticorum)</b> : a/w <b>IDDM</b> ; typically in obese middle-aged men, involving posterior neck and upper back	Histologically shows wide spaces between collagen bundles filled with mucin
Scleromyxedema	Progressive condition, characterized by widespread, symmetric, linearly distributed <b>waxy papules</b> , typically involving <b>face/neck</b> , dorsal hands, extensor forearms, elbows, and upper trunk; diffuse infiltration can mimic scleroderma and result in leonine facies; <b>histologically similar to NSF</b> , but fibrosis does not extend as deeply into subcutis and fascia; <b>extracutaneous involvement common</b> (GI: dysphagia; MSK: arthritis, proximal muscle weakness, carpal tunnel; neuro: peripheral neuropathy)	a/w <b>IgGλ</b> paraproteinemia and HIV
Pretibial myxedema	Waxy indurated nodules or plaques with a peau d'orange appearance on the <b>shins</b>	Due to deposition of hyaluronic acid, most commonly in <b>Grave's disease</b> , but may also be seen with hypothyroidism and rarely euthyroid patients
<i>Immunologic</i>		
Chronic GVHD	Morpheaform plaques on trunk, which may become generalized	Usually still see some degree of interface dermatitis histologically
<i>Paraneoplastic/Neoplastic</i>		
POEMS syndromes (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)	Sclerotic skin changes favoring extremities, <b>hyperpigmentation</b> , hypertrichosis, hyperhidrosis, digital clubbing, leukonychia	<b>Glomeruloid hemangiomas</b> are strongly associated (only present in a minority of patients)
Amyloidosis (primary systemic form)	Diffuse induration of face, distal extremities, and trunk	N/A
Carcinoid syndrome	Sclerotic skin on legs	N/A

Continued



**Table 3-15.** Other Sclerosing/Fibrosing Skin Disorders—cont'd

Disease	Clinical	Other
Carcinoma en cuirasse	Sclerodermoid induration of chest wall due to infiltration by cancerous cells	<b>Breast cancer</b> most commonly
<i>Metabolic</i>		
Diabetic cheiroarthropathy	Symmetric, painless loss of joint mobility, and stiffness of the small joints of the hand with scleroderma-like skin thickening of the dorsal aspects of the hands and feet; <b>“prayer sign”</b>	30%–50% of chronic DMII patients; correlates w/microvascular disease
Porphyria cutanea tarda	Morpheaform plaques in sun-exposed areas, hyperpigmentation, and hypertrichosis	Pseudoporphyria lacks sclerodermoid changes, hyperpigmentation, and hypertrichosis
<i>Diffuse Sclerodermoid Conditions due to Exogenous Substances</i>		
Toxic oil syndrome	p/w mobiliform eruption, <b>flu-like symptoms</b> , peripheral eosinophilia, and pulmonary edema; swelling and thickening of the skin occurs initially → followed by skin atrophy/fibrosis, dermal sclerosis, joint contractures, sicca symptoms, and Raynaud's phenomenon	Due to ingestion of aniline-degraded <b>rapeseed cooking oil</b> ; seen in <b>Spain</b> in 1981
Eosinophilia-myalgia syndrome	Presents initially with <b>fever, fatigue, weakness, severe myalgias</b> , peripheal <b>eosinophilia</b> , and a non-specific erythematous macular eruption; half develop sclerodermatous skin changes including eosinophilic fasciitis (30%), morphea, and diffuse/localized scleroderma	Due to ingestion of contaminated <b>L-tryptophan</b> , seen in 1989
Polyvinyl chloride	Workers exposed can develop skin findings that mimic scleroderma including diffuse sclerosis of the skin, sclerodactyly, Raynaud's phenomenon, and hepatic/pulmonary fibrosis	Absent autoantibodies
Bleomycin	<b>Pulmonary fibrosis</b> , <b>Raynaud's</b> phenomenon, and cutaneous changes indistinguishable from progressive systemic sclerosis	Absent autoantibodies
Taxanes (docetaxel, paclitaxel)	Diffuse edema (legs #1 site) → slowly becomes sclerotic; may result in flexion contractures	Absent autoantibodies; can occur after one or several courses of chemotherapy
Nephrogenic systemic fibrosis	Discussed in NSF section	a/w gadolinium-based contrast agents in setting of kidney disease
<i>Localized Sclerodermoid Conditions due to Exogenous Substances</i>		
Radiation-induced morphea	Morphea-like plaques in radiation field (sometimes extend beyond irradiated area); chest wall most common site	Most common in breast CA pts with history of XRT
Sclerosis at injection sites	<b>Vitamin K (Texier's disease)</b> , silicone or paraffin implants/injections, <b>intralesional bleomycin</b> , <b>opioids (methadone, pentazocine)</b>	Bleomycin may cause SSc-like diffuse eruption if used systemically

**Table 3-16.** Major Perforating Diseases

	Clinical	Histopathology	High-Yield Facts/Associations
Familial reactive perforating collagenosis (RPC)	Rare, <b>childhood</b> onset; M=F; upper extremities; keratotic papules develop at sites of trauma (3–4 wk latency); spontaneous resolution (6–10 wks)	Hyper-/parakeratotic crusted plug; <b>COLLAGEN</b> fibers extend through epidermis into plug	Sites of minor trauma Collagen perforates Upper extremities
Acquired perforating dermatosis (includes acquired RPC, Kyrle disease)	Common; <b>adult</b> onset; M=F; diabetes/ <b>renal failure</b> ; intense pruritis; <b>legs</b> or generalized; koebnerize; central keratotic plug	Resembles RPC most commonly (may also resemble perforating folliculitis or less commonly EPS)	Almost always a/w <b>diabetes</b> or <b>renal failure</b> (10% of dialysis patients) <b>Lower extremities</b> (extensor)
Elastosis perforans serpiginosa (EPS)	Rare; <b>childhood or early adulthood</b> ; <b>M</b> >F (4:1); annular/serpiginous plaques w/ <b>keratotic papules along rim</b> ; most commonly on <b>lateral neck</b> > face, arms, flexural areas	Keratotic crusted plug surrounding epithelial hyperplasia ( <b>“crab-claw”</b> ) grabbing pink elastic fibers in superficial dermis (VVG stain: elastic fibers stain black vs collagen pink)	<b>MAD</b> <b>Marfan's</b> <b>Acrogeria</b> <b>Down's</b> <b>PORES</b> <b>Penicillamine</b> , <b>PXE</b> <b>Osteogenesis imperfecta</b> <b>Rothmund-Thomson</b> <b>Ehlers-Danlos</b> <b>Scleroderma</b> May occur in Wilson's dz and cystinuria patients on <b>D-penicillamine</b>
Perforating calcific elastosis	Very rare; adulthood; mostly <b>black women</b> ; plaques on abdomen ( <b>periumbilical</b> ) with peripheral keratotic papules	Transepidermal elimination of calcified elastic fibers ( <b>PXE-like</b> )	Obese hypertensive <b>multiparous black women</b> Abdomen (especially periumbilical)

(Modified from Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

**Table 3-17.** Abnormalities of Connective Tissue

	Clinical Features	Histopathology	High-Yield Facts/Associations
Mid-dermal elastolysis	Uncommon; circumscribed areas of <b>fine wrinkling</b> ; symmetric on <b>trunk</b> , lateral neck, extremities; Caucasian <b>middle-aged females</b>	Normal H&E, elastic tissue stains demonstrate selective loss of elastic fibers in the <b>mid dermis only</b>	<b>UV light</b> may have role in pathogenesis
Anetoderma	1–2 cm areas of flaccid/wrinkled skin, usually <b>elevated</b> (>depressed or flat); neck, trunk, upper extremities; primary form F > M, 15–25 yo	Normal H&E, elastic tissue stain shows near complete loss of elastic fibers in <b>papillary and reticular</b> dermis; <b>fragmented</b> elastic fiber remnants visible	<u>Primary (idiopathic)</u> Jadassohn-Pellizzari (inflammatory) Schweneringer-Buzzi (non-inflammatory) <u>Secondary</u> Infection, penicillamine, inflammatory dermatosis, autoimmune ( <b>lupus</b> , Sjogren's, Graves' dz), cutaneous tumors
Follicular atrophoderma	Dimple-like follicular-based <b>"ice-pick"</b> depressions; <b>dorsal hands/feet and cheeks</b> ; onset birth to early childhood	Dilated follicles w/plugging, inflammation and dermal collagen sclerosis	<u>Associated with:</u> <b>Bazex-Dupre-Christol syndrome</b> (follicular atrophoderma, BCCs of face, milia, localized hypohidrosis above neck, hypotrichosis)
Atrophoderma vermiculatum	Variant of follicular atrophoderma that is on <b>face/cheeks exclusively</b> ; may be 1) sporadic, 2) inherited as a sole finding (AD), 3) part of a syndrome, or 4) presenting feature of KP-atrophicans	Same as above	<u>Associated with:</u> <b>Rombo syndrome</b> (atrophoderma vermiculatum, milia, acral erythema, peripheral vasodilation with cyanosis, multiple BCCs) <b>Nicolau-Balus syndrome</b> (generalized eruptive syringomas, atrophoderma vermiculata and milia) <b>Others:</b> Tuzun (scrotal tongue), and Braun-Falco-Marghescu (PPK and KP)
Striae	Atrophic linear lesions along cleavage lines violaceous in color, Caucasians; F > M	Clinical diagnosis	Puberty, pregnancy; <b>↑ in Marfan's syndrome</b>
Hypertrophic scar/keloids	Darker skin, often familial tendency; 10–30 yo; hypertrophic scar confined to wound borders and raised; Keloids delayed in onset, extend beyond wound borders	Hypertrophic scar: ↑fibroblasts/collagen oriented both parallel to skin surface like normal scar and in <b>whorled nodules</b> ; vertically oriented vessels Keloids: haphazardly-arrayed thick bundles of hyalinized collagen	Hypertrophic scars spontaneously resolve Keloids persist in absence of treatment; Rx: IL-steroids (first line), excision, XRT, topical imiquimod, lasers, IL, 5-FU

isomorphic Koebner response, insect bites, TBST, mycobacterial/viral infection, or UV radiation)

- Trigger → Th1 reaction → monocyte accumulation in dermis → release of lysosomal enzymes → degradation of elastic fibers
- Majority of affected patients are healthy (esp. localized GA)
  - Generalized GA more commonly a/w **hyperlipidemia** (up to 45%), **type I diabetes**, HIV, thyroid disease, and malignancy

#### Clinical features

- Benign, self-resolving condition that p/w asymptomatic **annular/arciform** plaques comprised of multiple small, **non-scaly**, flesh-colored to pink or violaceous papules
  - Solitary **umbilicated papules** are common presentation on **fingers/hands**
  - Previously involved skin in center of the **annulus** often has red-brown color
- Distribution: **isolated hands/arms most common** (60%; particularly dorsal hands/fingers and elbows) > isolated legs/feet (20%; particularly dorsal feet and ankles) > combined upper and lower extremities (7%)
  - Less commonly: isolated truncal lesions (7%) or trunk + other sites (5%)
- Variants:
  - **Patch GA**: symmetrical erythematous patches commonly on bilateral dorsal feet (or trunk and extremities); often lacks annular configuration; **histology shows interstitial GA** most commonly

- **Subcutaneous or deep dermal GA** ("pseudorheumatoid nodule"): most common in **children <6 yo**; large, asymptomatic rheumatoid-like nodules on **dorsal foot (#1 site)**, palms, shins, buttocks, and scalp; often a/w **trauma**; 50% also have classic GA lesions
- **Generalized (disseminated) GA**: occurs in minority of patients; later age of onset (40s–50s); comprised of innumerable small red-violaceous papules coalescing into **small annular plaques** especially on **upper trunk/proximal upper extremities** (Fig. 3-57); poor response to Rx; usually self-resolves over 3–4 years; **lipid abnormalities** in 45%; **diabetes** in 21% (vs only 10% in localized GA); ↑prevalence of HLA-Bw35
- **Perforating GA**: 5% of GA cases; most commonly on **dorsal hands and fingers**; small papules with central keratotic plug, umbilication, or ulceration; transepidermal elimination of degenerated collagen seen histologically
- **GA-like eruptions**: may be seen in association with solid organ tumors, B- and T-cell **lymphomas**, **HIV** (p/w generalized GA > localized), or at sites of **prior herpes zoster scars**

#### Histopathology

- All forms are characterized by granulomatous dermal inflammation with foci of collagen/elastic fiber degeneration, ↑mucin, and scattered eosinophils



**Figure 3-57.** Disseminated granuloma annulare. Numerous papules and small annular plaques. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- If LCV, granulomatous vasculitis or thrombosis is present, there is ↑risk of systemic disease (probably represents PNGD variant)
- Three common histologic patterns:
  - **Interstitial (most common; 70% of cases)**: most subtle pattern; singly-arrayed histiocytes between collagen fibers; minimal collagen/elastic fiber degradation; **key to diagnosis is ↑dermal mucin between collagen fibers** (best appreciated w/ Colloidal iron or Alcian Blue) and perivascular eosinophils
  - **Palisaded granulomas (25%)**: best visualized at low power; consist of one or more palisaded granulomas w/ central degeneration of collagen/elastic fibers and ↑dermal mucin
  - **Sarcoid pattern (5%)**: rare histologic presentation comprised of well-formed epithelioid histiocytic nodules
- Deep GA: palisaded granulomas w/ central blue-colored mucin (**vs pink fibrin in RA**) in deep dermis/SQ
- Perforating GA: typical GA findings, plus transepidermal elimination of degenerated collagen and granulomatous debris

#### Treatment

- Localized/asymptomatic: reassurance, **high potency topical or intralesional steroids**, TCIs, lasers, and light cryotherapy
  - In some cases, biopsy of lesion → resolution
- Severe disease: phototherapy, antimalarials, nicotinamide, isotretinoin, dapsone, pentoxifylline, PDT, **triple antibiotic regimens** (minocycline, ofloxacin, and rifampin), and **TNF-α inhibitors**

**Table 3-18.** IGDA/PNGD

IGDA	PNGD
Annular plaques or <b>linear red to skin-colored cords</b> (aka “ <b>rope sign</b> ,” usually in axilla)	<b>Umbilicated skin-colored to violaceous papules</b> +/- perforation/ulceration
Trunk, buttocks, and intertriginous areas (symmetric)	Symmetric involvement of <b>extensor digits, elbows</b> , and other extensors
Histology: small <b>rosettes</b> of palisading histiocytes in mid/deep reticular dermis (“bottom heavy”) around small foci (smaller than GA) of degenerated collagen; no mucin; +/-neutrophils; <b>no obvious vasculitis</b>	Histology: small vessel <b>LCV</b> w/ <b>basophilic collagen degeneration</b> (early) → palisaded granulomas with basophilic collagen degeneration +/- perforating collagen (late)
Most common associations: <b>RA</b> , seronegative arthritis, autoimmune thyroiditis, SLE Arthralgias or arthritis (50%)	Most common associations: <b>RA, SLE, ANCA + vasculitides</b> (Wegener’s/Churg-Strauss > others), malignancy

#### Prognosis/clinical course

- Spontaneous resolution in 2 years for half of patients
- 40% recurrence rate, but recurrent episodes clear faster

### Annular elastolytic giant cell granuloma (AEGCG, actinic granuloma of O’Brien, and atypical facial NLD)

- GA variant affecting **chronically sun-exposed skin** (face, neck, upper trunk, and arms)
- Possibly caused by inflammatory response to UV; most commonly middle-aged women
- Start as flesh-colored to pink papules → coalesce into **annular plaques** 1–10 cm in diameter; normally <10 total lesions
- Histopathology: interstitial (> well-formed palisaded) granulomatous infiltrate w/ more **multinucleated foreign body giant cells** than are typically seen in GA; **phagocytosed elastic fibers within histiocytes and giant cells (“elastophagocytosis”)**; no collagen alteration or lipid deposition, **lacks mucin**; **VVG stain shows absence of elastic fibers** and loss of solar elastosis in affected areas
- Rx: typically persistent; poor response to standard GA treatments

### Interstitial granulomatous dermatitis and arthritis (IGDA); and palisaded neutrophilic granulomatous dermatitis (PNGD)

- F > M
- These two granulomatous dermatitides exist on a spectrum (see [Table 3-18](#))
- Both are a/w systemic diseases:
  - **SLE and ANCA vasculitides** (PNGD > IGDA)
  - **RA** (both)
  - Other autoimmune diseases (both)
- Pathogenesis: autoimmune condition → immune complex deposition in/around dermal vessel walls→



chronic, low-intensity vasculitis (more brisk and neutrophil-rich in PNGD) → gradual impairment of blood flow to dermal collagen → collagen degeneration → palisaded granulomatous inflammation in reaction to degenerated collagen

- ANA(+) in 50%
- No specific treatment exists other than treating underlying disease, +/- topical or IL-steroids
- Two thirds of patients achieve complete remission (months to years); one third have persistent, chronic, relapsing course

### Interstitial granulomatous drug eruption

- Clinically may resemble interstitial GA, IGDA, or PNGD
  - Annular, red, non-scaly papules and plaques w/ indurated border; favors creases and often photodistributed; spares mucous membranes
- Most commonly caused by CCBs and ACE inhibitors (usually months to years after drug initiation)
  - Others: TNF- $\alpha$  inhibitors in RA patients, statins, furosemide,  $\beta$ -blockers, antihistamines, HCTZ, anakinra, and thalidomide
- Histology: may resemble interstitial GA, IGDA or PNGD but frequently has deeper dermal involvement (bottom two thirds of dermis), **interface dermatitis**, atypical lymphocytes, and lacks mucin
- Typically resolves months after drug discontinuation

### Necrobiosis lipoidica (necrobiosis lipoidica diabeticorum (NLD))

#### Epidemiology

- F > M (3:1)
- Only 0.03% of diabetics have NLD, but 22% of patients with NLD have or will develop **diabetes/glucose intolerance**
  - Diabetics w/ NLD have ↑ risk of peripheral neuropathy, retinopathy, and joint immobility
- May be a/w smoking

#### Pathogenesis

- Vascular compromise from immunodeposition in vessel walls or diabetes-related microangiopathic changes → subacute **dermal ischemia** → dermal collagen degeneration → secondary granulomatous inflammatory response

#### Clinical features

- Early lesions manifest as firm, reddish papules → expand into atrophic plaques (usually multiple) on bilateral **shins** w/ a peripheral violaceous to **erythematous rim** and **atrophic central yellow-brown discoloration** w/ **telangiectasias** (Fig. 3-58)
  - Minor trauma results in **ulceration** (30%)
- Adnexae and neural elements frequently lost within NLD plaques → ↓ pinprick/fine touch sensation, hypohidrosis, and localized alopecia

#### Histopathology

- "Square biopsy" sign
- **Horizontally arranged ("layered") palisaded granulomatous inflammation** w/ horizontal tiers of degenerated collagen fibers (irregular size and shape) and dermal sclerosis
- Process **diffusely involves entire dermis** and subQ fat septae (vs GA, which tends to have patchy, predominantly superficial dermal inflammation)
- Lacks mucin
- **Plasma cells** and multinucleated GCs are abundant (both uncommon in GA)
- +/- epidermal atrophy; +/- vascular hyalinization (Fig. 3-59)

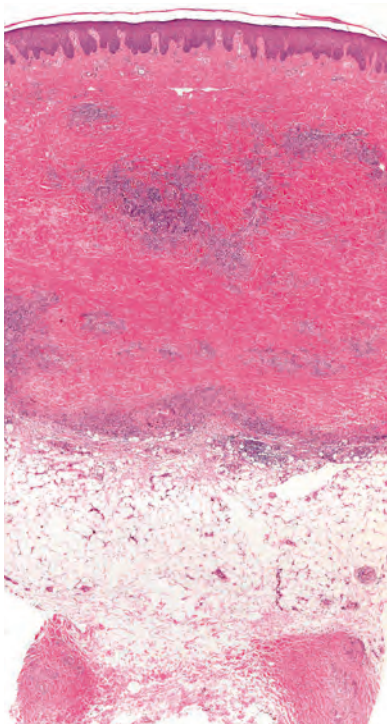
#### Treatment

- First line: **potent topical and/or intralesional steroids** (injected into inflammatory rim); TCIs (early lesions)
- Systemic steroids, colchicine, cyclosporine, TNF- $\alpha$  inhibitors, CO<sub>2</sub> laser, stanozolol, and pentoxifylline in chronic/recalcitrant cases



**Figure 3-58.** Necrobiosis lipoidica. Red-brown atrophic plaques on anterior shins. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)





**Figure 3-59.** Necrobiosis lipoidica – histologic features. Multiple granulomas within the entire dermis extending into the subcutaneous fat. Note the layered tiers of granulomatous inflammation aligned parallel to the skin surface. Courtesy, Lorenzo Cerroni, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

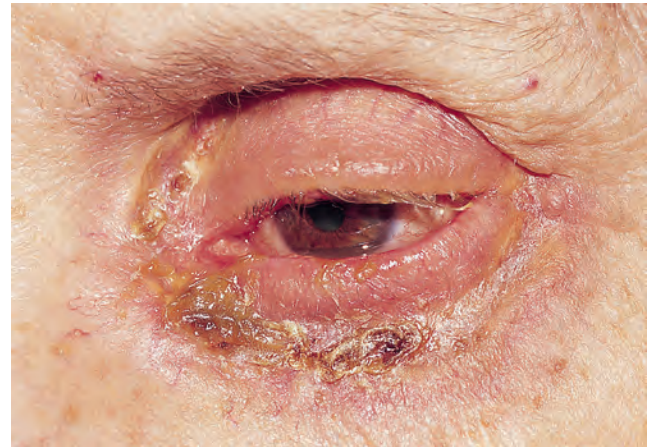
- Surgical excision to fascia w/ skin grafting may be necessary in severe ulcerative cases

#### Prognosis/clinical course

- Rarely undergoes spontaneous remission (17% at 8–12 years)
- Control of blood glucose levels does **not** affect disease course
- No treatment has demonstrated efficacy in large double-blind studies
- SCC may arise in chronic ulcerative lesions

### Necrobiotic xanthogranuloma (NXG)

- Peak in sixth decade; M = F
- Multisystem histiocytic disease that p/w firm **yellow xanthomatous** plaques and nodules, most commonly in **periorbital** region (Fig. 3-60) (> trunk, proximal extremities)
  - Often **ulcerates** and leads to scarring
- 50% have ophthalmic manifestations (ectropion, keratitis, uveitis, and proptosis); majority also have endocardial involvement; hepatosplenomegaly common
- Strongly a/w **IgGκ monoclonal gammopathy** (due to plasma cell dyscrasia or multiple myeloma)
  - Skin findings precede diagnosis of malignancy by 2–20 yrs
- Histopathology: diffuse (pandermal and into subcutis), palisading **xanthogranulomas** w/ necrobiotic collagen,



**Figure 3-60.** Necrobiotic xanthogranuloma in a patient with a paraproteinemia. (From Callen JP, et al. *Dermatological Signs of Internal Disease* 4th ed. Elsevier. 2009)

foamy histiocytes, “dirty dermis” (scattered inflammatory cell debris), **abundant cholesterol clefts**, and multiple Touton and **bizarre foreign body GCs** (HUGE multinucleated cells w/ “horse-shoe” arrangement of 25–50 nuclei → these cells are not seen in NLD or GA)

- Rx: none effective; treat underlying malignancy or paraproteinemia

### Cutaneous Crohn’s disease

#### Epidemiology

- 20%–45% of Crohn’s patients have skin or mucosal findings
- **Crohn’s specific (uncommon)**: contiguous perianal/genital/oral Crohn’s, distant (“metastatic”) Crohn’s
- **Non-specific/reactive (more common)**: **erythema nodosum**, **pyoderma gangrenosum** (UC > Crohn’s), pyostomatitis vegetans (UC > Crohn’s), pathergy (pustular response to trauma), **EB acquisita** (IBD is most common cause of EBA), and acrodermatitis enteropathica-like syndrome due to zinc deficiency
- F > M; average age = 35 yo
- Cutaneous Crohn’s is more frequently a/w colorectal rather than small intestinal disease
- Skin findings may precede GI diagnosis of Crohn’s (20% of cases)

#### Pathogenesis

- Genetic predisposition + defective microbial clearance, mucosal compromise or altered gut flora balance (dysbiosis) → exaggerated Th1 and Th17 response to gut flora → granulomatous lesions in gut and skin

#### Clinical features

- **Genital Crohn’s**: **labial or scrotal edema** + erythema/ulceration/fissures (Fig. 3-61)
- **Perianal Crohn’s**: **ulcers**, **sinus tracts**, **fissures**, or eroded vegetating plaques; lesions frequently extend to



**Figure 3-61.** Cutaneous Crohn's disease. Note the swelling and violaceous discoloration of the labia majora in this prepubescent girl. Courtesy, Joseph L Jorizzo, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

perineum, buttocks, abdomen, and abdominal surgical or ostomy sites

- Peristomal Crohn's: fissures and fistulae around ostomy
- **Oral Crohn's:** "cobblestoning" of buccal mucosa, pyostomatitis vegetans, **cheilitis granulomatosa**, gingival hyperplasia, diffuse oral swelling, fissures, aphthous-like ulcers, linear ulcers, and small gingival nodules
- **Extragenital ("metastatic") Crohn's:** dusky red papules/plaques → ulcerations with undermined edges, fistulas, draining sinuses and scarring; most common sites = **lower extremities/soles** (38%) > abdomen/trunk (24%) > upper extremities (15%), face/lips (11%), flexures (8%), generalized (4%)

#### Histopathology

- Non-caseating tuberculoid granulomas w/ inflammatory rim of lymphocytes in superficial and deep dermis; frequent Langerhan's GCs

#### Treatment/prognosis

- First line: oral metronidazole, topical/intralesional steroids, and TCIs
- Severe cases: oral steroids, sulfasalazine, MTX, MMF, cyclosporine, thalidomide, azathioprine, 6-MP, and TNF- $\alpha$  inhibitors
- Disease tends to be chronic; severity of cutaneous and GI disease often not correlated

## Sarcoidosis

#### Epidemiology

- Bimodal incidence peaks: 25–35 yo and 45–65 yo
- F > M
- **African Americans** have highest incidence and disease tends to be more severe/progressive
- ↑incidence of cases in spring and winter → environmental/infectious trigger hypothesis



**Figure 3-62.** Sarcoidosis characteristic papules on the nares. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

#### Pathogenesis

- Multisystem granulomatous disease caused by upregulation of CD4+ Th1 cells:
- Genetic predisposition + **unknown antigen** presented by monocytes with MHC class II molecules → activation of CD4+ Th1 cells → ↑IL-2, IFN- $\gamma$ , TNF- $\alpha$ , and monocyte chemotactic factor (MCF) → monocytes leave circulation and enter peripheral tissues, including skin, where they form granulomas → granulomas have potential to result in end-organ dysfunction
- Drug-induced sarcoid:
  - **Hepatitis C pts on treatment (IFN- $\alpha$ , ribavirin)**
  - HIV pts on HAART
  - Other meds: TNF- $\alpha$  inhibitors, vemurafenib, ipilimumab, and alemtuzumab

#### Clinical features

- 35% of patients with sarcoidosis develop skin lesions
  - Skin may be the only site of involvement
  - All pts w/ cutaneous sarcoid require CXR, PFTs, and regular eye exams
- Present as red-brown or erythematous papules and plaques w/ characteristic "**apple jelly**" color with diascopy (better appreciated on light-skinned patients)
  - Lesions typically lack secondary changes
  - Predilection for **face** (**Fig. 3-62**) (especially **lips and nose**), neck, and upper half of the body
  - Lesions often arise within preexisting scars, piercings, or tattoos
  - Less common presentations: hypopigmented, ichthyosiform, angiolupoid (prominent telangiectasias), psoriasiform, annular, verrucous, cicatricial alopecia, and erythrodermic
- **Erythema nodosum:** most important non-specific manifestation of sarcoidosis since it predicts a **benign, self-limited course**
- Other areas of involvement:
  - **Lung disease (90%):** alveolitis, bronchiolitis, and pleuritis; may culminate in "**honeycombing**" of lung, w/ fibrosis and bronchiectasis
  - **Lymphadenopathy (90%):** hilar and/or paratracheal; typically asymptomatic

**Table 3-19.** Sarcoid Variants

Lupus pernio	<b>Violaceous</b> (rather than red-brown) papules coalescing into infiltrative plaques; <b>nose/earlobes/cheeks</b> = most common sites; <b>"beaded" appearance</b> along nasal rim (Fig 3-63); resolves with scarring (unlike most cutaneous sarcoid); <b>strongly a/w chronic sarcoid lung (75%) and upper respiratory tract (50%) disease</b> , cystic degeneration of bones of distal phalanges, ocular involvement, and reticuloendothelial involvement; rarely involutes and has <b>poor prognosis</b>
Darier-Roussy	<b>Subcutaneous sarcoid</b> ; painless, firm, deep-seated mobile nodules; 90% have hilar adenopathy and multiple lesions; a/w <b>good prognosis</b>
Löfgren's syndrome	<b>Acute</b> form of sarcoidosis; p/w <b>erythema nodosum + hilar adenopathy</b> + fever + migrating polyarthritis + acute iritis; most common in <b>Scandinavian whites</b> , rare in blacks; a/w <b>good prognosis</b>
Heerfordt's syndrome ("uveoparotid fever")	<b>Uveitis + parotid gland enlargement + fever + cranial nerve palsy</b> (facial nerve most commonly)
Mikulicz's syndrome	Outdated, non-specific term (may be seen in TB, sarcoid, Sjögren's syndrome, lymphoma), referring to enlargement of salivary, lacrimal, and parotid glands
Blau syndrome	<b>Early-onset</b> (age <5 yo) sarcoid-like disease; caused by <b>NOD2 mutation</b> ; triad of skin, eye, and joint dz
Drug-Induced cutaneous sarcoid	<b>IFN-<math>\alpha</math> (hepatitis C patients)</b> , HIV pts on HAART, TNF- $\alpha$ inhibitors

- **Ocular involvement (20%–50%): anterior uveitis** (most common), retinitis, lacrimal inflammation, and conjunctivitis → may result in blindness
- **Hypercalcemia (10%):** due to **calcitriol synthesis by sarcoidal granulomas** (convert 25-hydroxyvitamin D to more active 1,25-dihydroxyvitamin D) → hypercalcemia, hypercalciuria, and **nephrocalcinosis** → renal failure
- **Other:** nail changes (clubbing, onycholysis, and subungual hyperkeratosis), oral involvement (salivary gland, gingiva, hard/soft palate, and tongue), liver, and heart involvement
- Sarcoid variants (Table 3-19)

#### Histopathology

- Superficial and deep dermis packed w/ nodules of **well-formed, non-caseating, "naked epithelioid granulomas"** (epithelioid granulomas lacking a significant inflammatory rim of lymphocytes or plasma cells)
  - **Asteroid bodies** (star-shaped eosinophilic inclusions of collagen) and Schaumann bodies (basophilic calcium and protein inclusions) are commonly seen within histiocytic GCs

#### Laboratory testing

- **Kveim-Siltzbach test** (not routinely performed): injecting suspension of sarcoidal spleen into the skin of a patient w/ sarcoidosis → sarcoidal granuloma at injection site



**Figure 3-63.** Sarcoidosis – clinical variants. Coalescing violaceous papules on the nose in lupus pernio; note the notching of the nasal rim. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- CXR or CT scan (most sensitive): hilar/paratracheal lymphadenopathy +/- pulmonary infiltrates
- PFTs: restrictive lung disease pattern → ↓total lung capacity, ↓diffusing capacity, and ↓vital capacity
- ↑ACE level (60%; more useful in **monitoring** response to treatment than for diagnosis)
- ↑ESR; hypercalcemia, lymphopenia

#### Treatment

- First line: **oral prednisone** for systemic involvement +/- topical or IL-steroids for skin involvement; the degree of lung, eye, and other internal involvement determines how quickly you can taper prednisone
- Most effective treatment for chronic skin-predominant disease: hydroxychloroquine and chloroquine
- Others: TNF- $\alpha$  inhibitors, MMF, azathioprine, minocycline, and leflunomida

#### Additional Boards Factoids

- **Granulomatous Dermatitis Summary** (Fig. 3-64), (Table 3-20), and (Table 3-21)

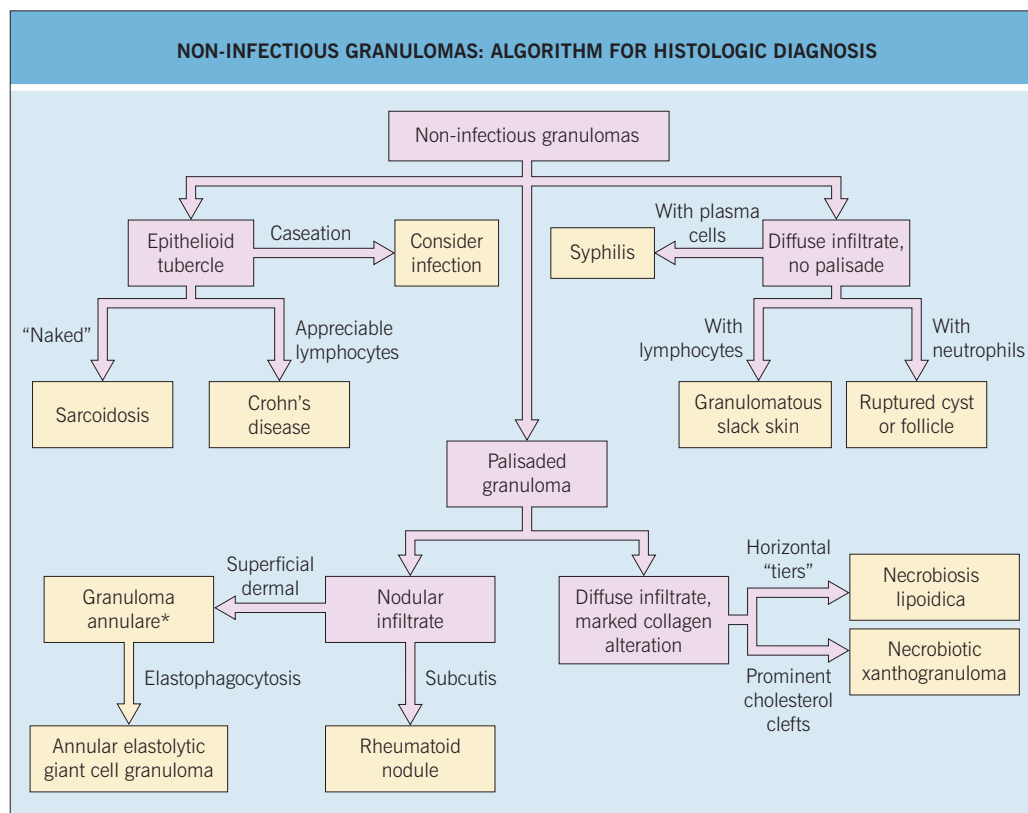
#### Foreign body reactions (Table 3-22) and (Table 3-23)

- Non-organic and high molecular weight organic materials that are deposited into the dermis/subcutis and are resistant to biologic degradation by inflammatory cells may give rise to a foreign body reaction
- p/w indurated red or red-brown papules coalescing into plaques +/- ulceration
- Histopathology: foreign body granulomas +/- recognizable foreign material
- Less common reaction patterns: pseudolymphomatous, lichenoid, and eczematous

#### Histiocytoses

- Group of proliferative disorders that share a common CD34+ progenitor cell in bone marrow





**Figure 3-64.** Non-infectious granulomas: algorithm for histologic diagnosis. Interstitial granulomatous dermatitis and palisaded neutrophilic and granulomatous dermatitis may represent an additional diagnostic consideration. \*May also have a patchy dermal interstitial pattern without palisades, or subcutaneous palisades with more mucin than rheumatoid nodules. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 3-20.** Clinical Features of the Major Granulomatous Dermatitides

	<b>Sarcoidosis*</b>	<b>Classic Granuloma Annulare<sup>†</sup></b>	<b>Necrobiosis Lipoidica</b>	<b>AEGCG</b>	<b>Cutaneous Crohn's Disease</b>	<b>Rheumatoid Nodule</b>
Average age (years)	25–35, 45–65	<30	30	50–70	35	40–50
Sex predilection	Female	Female	Female	None	Female	Male <sup>‡</sup>
Racial/ethnic predilection in US	African-American	None	None	Caucasian	Ashkenazi Jews	None
Sites	Symmetric on face, neck, upper trunk, extremities	Hands, feet, extensor aspects of extremities	Anterior and lateral aspects of distal lower extremities	Face, neck, forearms (sites of chronic sun exposure)	Genital areas, lower > upper extremities	Juxta-articular areas, especially elbows, hands, ankles, feet
Appearance	Red to red-brown papules and plaques; occasionally violaceous or annular	Papules coalescing into annular plaques	Plaques with elevated borders, telangiectasias centrally	Annular plaques	Dusky erythema and swelling, ulceration	Skin-colored, firm, mobile subcutaneous nodules
Size of lesions	0.2 to >5 cm	1–3 mm papules, annular plaques usually <6 cm	3 to >10 cm	1–6 cm	Variable	1–3 cm
No. of lesions	Variable	1–10	1–10	1–10	1–5	1–10
Associations	Systemic manifestations of sarcoidosis; INF- $\alpha$ therapy for hepatitis C viral infection >> melanoma	Rare diabetes mellitus, HIV infection, malignancy	Diabetes mellitus	Actinic damage	Intestinal Crohn's disease	Rheumatoid arthritis
Special clinical characteristics	Occasional central atrophy and hypopigmentation; development within scars	Central hyperpigmentation	Yellow-brown atrophic centers, ulceration	Central atrophy and hypopigmentation	Draining sinuses and fistulas	Occasional ulceration, especially at sites of trauma

AEGCG, annular elastolytic giant cell granuloma; HIV, human immunodeficiency virus

\*Clinical variants include lupus pernio and subcutaneous (Darier-Roussy), psoriasiform, ichthyosiform, angiolioid, and ulcerative sarcoidosis.

<sup>†</sup>Clinical variants include generalized, micropapular, nodular, perforating, subcutaneous, and patch granuloma annulare.

<sup>‡</sup>Although rheumatoid arthritis has a female:male ratio of 2–3:1.

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Table 3-21.** Histologic Features of the Major Granulomatous Dermatitis

	<b>Sarcoidosis</b>	<b>Granuloma Annulare</b>	<b>Necrobiosis Lipoidica</b>	<b>AEGCG</b>	<b>Cutaneous Crohn's Disease</b>	<b>Rheumatoid Nodule</b>	<b>Interstitial Granulomatous Dermatitis*</b>	<b>Palisading Neutrophilic and Granulomatous Dermatitis*</b>
Typical location	Superficial and deep dermis†	Superficial and mid dermis†	Entire dermis, subcutis	Superficial and mid dermis	Superficial and deep dermis	Deep dermis, subcutis	Mid and deep dermis	Entire dermis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial	Diffuse palisading and interstitial; horizontal "tiers"	Palisading, irregular	Tubercle with surrounding lymphocytes	Palisading	Palisading in small "rosettes"	Palisading; prominent neutrophils and leukocytoclasia
Necrobiosis (altered collagen)	No	Yes ("blue")	Yes ("red")	No	No	Yes ("red")	Yes ("blue")	Yes ("blue")
Giant cells	Yes	Variable	Yes	Yes	Yes	Yes	Variable	Variable
Elastolysis	No	Variable	Variable	Yes	No	No	Variable	Variable
Elastophagocytosis	No	No	No	Yes	No	No	No	No
Asteroid bodies	Yes	Variable	Variable	Yes	No	No	Variable	Variable
Mucin	No	Yes	Minimal	No	No	Variable	Minimal	Variable
Extracellular lipid	No	Variable	Yes	No	No	Variable	No	No
Vascular changes	No	Variable	Yes	No	No	Yes	No	Yes

*\*Interstitial granulomatous dermatitis and palisading neutrophilic and granulomatous dermatitis are often considered two ends of a spectrum. AEGCG, annular elastolytic giant cell granuloma*  
*(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)*

**Table 3-22.** Foreign Body Reactions

<b>Foreign Body</b>	<b>Clinical Presentation</b>	<b>Histopathology</b>	<b>Other Key Points</b>
Tattoo inks	Red tattoos ( <b>mercuric sulfide</b> , aka <b>cinnabar</b> ) are most common cause of delayed reactions, usually lichenoid or pseudolymphomatous papules and nodules Eczematous dermatitis <b>Photoallergic reactions</b> , usually to <b>yellow ink (cadmium sulfide)</b> , red ink (cadmium selenide) or yellow-red (azo dyes)	<b>Lichenoid</b> dermatitis or <b>pseudolymphoma</b> (red tattoo) Spongiotic dermatitis (many others) Granulomatous ( <b>aluminum</b> , and others)	Tattoo pigment granules in dermis are smaller and darker than endogenous pigments (hemosiderin and melanin) <u>Various Q-switched lasers are ToC for tattoos:</u> QS-ruby (694 nm), QS-alexandrite (755 nm), QS-Nd:YAG (1064 or 532 nm) Ruby, alexandrite, and Nd:YAG (1064 nm) all treat <u>black, blue, dark brown</u> Ruby or alexandrite is ToC for <u>green</u> Only frequency-doubled Nd:YAG (532 nm) is effective for <u>red, yellow, light brown, violet, and white</u> If tattoo is inflamed, excise (instead of laser) to ↓risk of systemic allergic rxn
Silica (silicon dioxide)	Penetrating injuries involving <b>sand, soil, rocks, glass</b> ; prolonged incubation period (up to 25 yrs); p/w nodules, indurated plaques within scar Disseminated papules (blast injuries)	Sarcoidal granulomas containing <b>colorless, birefringent crystals</b>	Rx: excision
Talc (hydrous magnesium silicate)	Common component of <b>dusting powders</b> (umbilical stump, intertriginous areas of obese pts), surgical glove lubricants, and as filler for med tablets (IV drug abusers who mash up meds and inject) p/w sarcoid-like papules; may appear pyogenic granuloma-like	Sarcoidal or foreign body granulomas with needle-shaped or round crystals that are white and <b>birefringent on polarized light</b>	On H&E, the color of the needle-shaped or round talc crystals is highly variable (clear, blue-green or yellow-brown) Rx: excision
Zirconium	Zirconium in <b>antiperspirants</b> → persistent, soft brown papules in axilla	Sarcoidal granulomas; <b>no polarizable particles</b> seen	Zirconium particles are too small to be seen by polarized light microscopy → need advanced X-ray/electron imaging techniques Rx: excision

**Table 3-22.** Foreign Body Reactions—cont'd

Foreign Body	Clinical Presentation	Histopathology	Other Key Points
Beryllium	Used in manufacturing of <b>fluorescent lights</b> in the past; could result in systemic or local reactions: Systemic berylliosis: industrial exposure via inhalation → granulomatous lung disease with rare skin involvement (<1%) by scattered sarcoidal papules Localized cutaneous Berylliosis: puncture wound by fluorescent bulb → slowly-healing nodules/ulcers	Caseating granulomas (localized cutaneous form); <b>no polarizable particles</b> seen	<b>Bronchioalveolar lavage recommended for Dx of systemic berylliosis</b> Beryllium particles are too small to be seen by polarized light microscopy → need advanced X-ray/electron imaging techniques Rx: excision
Aluminum	Persistent subcutaneous nodules at <b>vaccine injection sites</b> ; arise several months after vaccination	Granulomas with central granular debris and palisade of surrounding histiocytes; <b>no polarizable particles</b> seen	Topical aluminum chloride for hemostasis can give similar stippled appearance to histiocytes in healing wound Aluminum particles are too small to be seen by polarized light microscopy → need advanced X-ray/electron imaging techniques Rx: excision
Zinc	Rare injection-reaction due to zinc-containing insulin shots; p/w furuncles at injection sites → heals with atrophic scars	Dense neutrophilic infiltrate with <b>birefringent rhomboidal crystals</b> → granulomas and fibrosis (end-stage)	Rx: excision
Starch	Due to contamination of wounds from <b>surgical gloves</b> with starch lubricant; p/w papules, nodules	Foreign body granulomas with <b>ovoid basophilic starch granules</b> that stain <b>PAS+</b>	
Cactus ( <i>Opuntia</i> is most common genus)	Clusters of dome-shaped, skin-colored papules with a central black dot; occurs in those who peel/sell <b>prickly pear fruit</b>	Sarcoidal or foreign body granulomas w/ <b>PAS+ spines</b> (extra- and intracellular)	
Jellyfish, corals, sea urchin spines	Pruritic lichenoid papules and plaques (onset 2–3 wks after exposure) <b>Linear, zig-zag, and whip-like (flagellate)</b> patterns of erythema/edema (early), hyperpigmentation or lichenoid papules (late)	Lichenoid dermatitis	May see birefringent calcite crystals (sea urchin spines) Rx: IL-steroids for delayed-type reactions
Keratin	Ruptured epidermoid cysts Pseudofolliculitis/acne keloidalis Pyogenic granuloma-like lesions, ingrown nails Pilonidal sinus	Foreign body granulomas w/birefringent keratin debris	
Intralesional corticosteroids	Due to failure of dispersion of injected material → weeks to months later develop FB rxn Skin-colored to yellow-white papules at site of prior IL-steroid injection	Foreign body granulomas with central <b>pale bluish material</b> (resembles mucin) on H&E	
Suture	Inflamed papule in wound that opens to form a fistula	Foreign body granulomas with <b>birefringent suture material</b>	

(Adapted from Table 94.3 in Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)**Table 3-23.** Distinguishing Staining Characteristics of Foreign Body Granulomas

Birefringent		Non-Birefringent
PAS (+)	PAS (–)	
Starch, cactus spines, wood splinters	Silica, talc, zinc, keratin, sea urchin spines, sutures, arthropod parts	Aluminum, beryllium, zirconium

- This common ancestor later differentiates into a variety of so-called “histiocytes”:
  - **Langerhans cell**: potent APC that migrates to and from epidermis, stains positively with **CD1a**, **S100**, and **Langerin** (**CD207** is most specific, stains Birbeck granules); has pathognomonic intracytoplasmic **Birbeck granules on electron microscopy**
  - **Mononuclear cell/macrophage**: migrates to and from **dermis**, has phagocytic and APC abilities, and stains positively w/ **CD68** and **HAM56**
  - **Dermal dendrocyte/dendritic cell (two types exist)**:
    - Type 1 dermal dendrocyte: versatile **factor XIIIa<sup>+</sup>** cell; resides in papillary dermis; involved in antigen presentation, phagocytosis, collagen production, and wound healing
    - Type 2 dermal dendrocyte: less known about this **CD34<sup>+</sup>** cell; resides in reticular dermis
- Abnormal proliferation of any of these histiocyte cell types leads to the various forms of histiocytosis (**Table 3-24** and **Table 3-25**)
- There is a high degree of clinical and histopathologic overlap between entities within a group (i.e., the various non-LCHs are very similar to each other, but all are different than LCH)

**Table 3-24.** Langerhans Cell Histiocytosis

**BRAF V600E mutation (60%)** and MAP2K1 mutations → ERK activation plays a role

**S100+, CD1a+, Langerin+**

Negative for factor XIIIa, CD68, and HAM56

**Histology:** dense proliferation of Langerhans cells with **reniform nuclei** and eosinophils in papillary dermis, with single and nested **LCH cells in the epidermis**

	Age (yrs)	Clinical Presentation	Other High-Yield Facts
Letterer-Siwe	Always before 2 yo	Acute, <b>disseminated</b> , visceral, and cutaneous lesions; p/w 1–2 mm pink <b>seborrheic papules</b> /pustules/vesicles on <b>scalp</b> , <b>flexural</b> neck/axilla/perineum, trunk; petechiae, purpura, scale, crust, erosion, impetiginization, and tender fissures common	<b>Poor prognosis</b> ; extensive visceral and painful osteolytic bone lesions; thrombocytopenia and anemia = poor prognosis Clues to Dx = scalp papules are more <b>discrete</b> than in seb derm (Fig. 3-65), <b>petechiae</b> , and <b>purpura</b> ; not typical in seb derm
Hand-Schüller-Christian	2–6 yo	<b>Triad</b> : diabetes insipidus, osteolytic bone lesions (cranium), exophthalmos (least common); skin lesions (30%) have similar distribution as Letterer-Siwe	Diabetes insipidus usually irreversible; manage with <b>vasopressin</b> ; bone lesions cured w/ curettage
Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker)	Starts at birth to few days after	<b>Skin-limited form</b> , rapidly self-healing; widespread (>solitary) red or purple-brown papulonodules +/- erosion → crust and resolve weeks later	Rapid spontaneous resolution, but patients should be followed closely
Eosinophilic Granuloma	Older children (7–12 yo)	Localized form of LCH; solitary, usually asymptomatic <b>bone</b> lesions (cranium > ribs, spine, long bones); very rarely involves skin or mucosa	Spontaneous fracture often the presenting sign; bone lesions cured w/curettage

**Table 3-25.** Non-Langerhans Cell Histiocytoses

- **All are CD68+**, +/-Factor XIIIa
- **All are negative for Langerin**
- S100 is negative in all except ICH and Rosai-Dorfman
- CD1a is negative in all except ICH

	Age (years)	Clinical Presentation	Other High-Yield Facts
<b>Primarily cutaneous, Self-resolving</b>			
JXG	0–2 (15% at birth, 75% in 1 <sup>st</sup> year of life)	<b>One</b> to few lesions >> numerous/widespread; pink to red/yellow; <b>head/neck</b> > upper trunk, extremities (Fig. 3-66); mucosal JXG is rare; Unilateral eye involvement in 0.5% ( <b>iris</b> most common) → hyphema, glaucoma → blindness	Spontaneous resolution in 3–6yrs; Rare visceral lesions; 40% of pts with ocular involvement also have skin involvement <b>Risk factors for ocular involvement</b> : multiple cutaneous JXGs and children <2yrs <b>“Triple association” of JXG, NF-1 and &gt;20x ↑ risk of juvenile myelomonocytic leukemia (JMML)</b> Histology: Well-circumscribed, dense dermal infiltrate of foamy lipidized histiocytes, <b>Touton giant cells</b> and eosinophils; loss of rete ridges +/-ulceration
Benign Cephalic Histiocytosis (likely a JXG variant)	Infants (<1 yo usually)	Numerous (more lesions than typical JXG) red-brown macules & papules of <b>face/neck</b> (Fig. 3-67) that may progress to upper torso	<b>Self-limited</b> <b>No internal or mucosal involvement</b> Historically known for intracytoplasmic “comma-shaped/worm-like” bodies on electron microscopy (not specific); Histology: very similar to JXG but <b>no Touton giant cells</b> , minimal-to-no lipidized histiocytes
Generalized Eruptive Histiocytosis (likely a JXG variant)	<b>Adults</b> (20–50yo) > kids	Recurrent eruption of hundreds of small (<1cm) red-brown papules in <b>axial</b> distribution (trunk, proximal extremities > face); heal with hyperpigmentation	<b>Self-limited; no internal or mucosal involvement</b> Histology: Same as BCH → clinical distinction required
Indeterminate Cell Histiocytosis (ICH)	Any	Solitary and generalized variants exist; trunk, extremities; eruption clinically and histologically indistinguishable from BCH and GEH → need immunostains to distinguish	Rare visceral and bone lesions with occasional fatal cases <b>S100(+)</b> and <b>CD1a(+)</b> like LCH <b>Langerin(-)</b> since no Birbeck granules → differentiates from LCH
<b>Cutaneous + frequent systemic involvement</b>			
NXG	50s	Destructive multisystem disease; Yellow xanthomatous plaques +/- ulceration; <b>Periorbital</b> >> other face, trunk, extremities; <b>50% have ophthalmic complications</b> ; hepatosplenomegaly, leukopenia and ↑ESR	<b>IgGκ monoclonal gammopathy</b> (>80%), a/w plasma cell dyscrasia or multiple myeloma Histology: See NXG section.
Reticulohistiocytosis (Multicentric Reticulohistiocytosis and solitary reticulohistiocytoma)	30s–40s (very rare in kids)	<b>Multicentric form</b> : F>M; Red-brown or yellow nodules; Acral sites favored ( <b>head, dorsal hands</b> >elbows) (Fig. 3-68); 50% have <b>oral or nasopharyngeal</b> lesions; severe <b>destructive arthritis</b> → arthritis mutilans (45%); no effective treatment <b>Solitary form</b> : Solitary, asymptomatic <1cm yellow-red nodule; head (#1 site); young adults (M=F); no systemic involvement; self-resolving but may excise	Multicentric form: ↑ESR, fever, anemia; <b>Solid organ malignancy in 30%</b> <b>“Coral bead”</b> appearance = papules along periungual region Histology: Dermal infiltrate of mono- and multi-nucleated histiocytes with granular, pink-purple (aka amphophilic, “ground glass”) cytoplasm, often surrounded by empty white spaces ( <b>lacunae</b> )

**Table 3-25.** Non-Langerhans Cell Histiocytoses—cont'd

	Age (years)	Clinical Presentation	Other High-Yield Facts
Rosai-Dorfman	10–30	Multisystem disease of children or young adults; massive but asymptomatic <b>bilateral cervical lymphadenopathy</b> ; fever/night sweats/weight loss; ↑ESR, polyclonal hypergammaglobulinemia; <b>any internal organ may be involved</b> ; 10% have skin lesions (#1 sites = <b>eyelids</b> and <b>malar</b> cheek); p/w multiple red-brown or xanthomatous papules/plaques; disease <b>usually self-resolves</b>	↑Incidence in West Indians Histology: pan-dermal infiltrate of very large, very foamy <b>S100<sup>+</sup>/CD68<sup>+</sup> histiocytes with emperipolesis</b> (engulfment of intact lymphocytes and plasma cells), abundant <b>plasma cells</b> Skin-limited form: benign; usually pts are older and female (systemic involvement more often seen in males and younger pts)
Xanthoma Disseminatum	<25 (60%), but any age	<b>Triad</b> : Cutaneous xanthomas, mucosal xanthomas (oral and upper airway most commonly), diabetes insipidus p/w 100s of red-brown or yellow papules → coalesce into <b>oddly-patterned xanthoma-like plaques</b> (Fig. 3-69); symmetric <b>flexural/intertriginous</b> involvement	Normolipemic; a/w <b>monoclonal gammopathy, plasma cell dyscrasia</b> ; Histology: Dense dermal infiltrate of many foam cells and occasional Touton giant cells; chronic course; no effective treatment
<b>Systemic, usually without skin involvement</b>			
Erdheim-Chester	Any	Fever, <b>bone lesions</b> , diabetes insipidus, exophthalmos, CNS, multiple internal organs; Skin involvement in minority (25%); eyelids and upper half of body; red-brown to yellow indurated nodules/plaques	<b>High mortality rate</b>



**Figure 3-65.** Langerhans cell histiocytosis, seborrheic dermatitis-like eruption with hemorrhage. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)



**Figure 3-66.** Juvenile xanthogranuloma, multiple nodules. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

## Langerhans cell histiocytosis

- Prognosis is primarily determined by extent of systemic involvement
  - New classification systems classify LCH according to degree of systemic involvement
  - However, the old classification scheme (see Table 3-24) may still be relevant for Boards purposes
- Progression of skin-limited disease to systemic involvement is uncommon
- If a patient has multisystem disease, but >2 years old and no involvement of liver, lungs, spleen, or hematopoietic system, then 100% survival is likely
- Features predictive of poor prognosis: **BRAF V600E mutation** and failure to respond to treatment by 6 weeks

## Non-Langerhans cell histiocytoses (discussed in Table 3-25)

## 3.7 MONOCLONAL GAMMOPATHIES OF DERMATOLOGIC INTEREST

- Monoclonal gammopathies often arise in setting of plasma cell dyscrasia or multiple myeloma
- Their associations w/ various dermatoses is an exam favorite (Table 3-26)

## 3.8 XANTHOMAS

- Intracellular and dermal lipid deposition → yellow appearance of lesions
- Prefer skin, tendons, and eyes
- Due to abnormalities in lipid metabolism (primary or secondary; may be a/w atherosclerosis) or **monoclonal**





**Figure 3-67.** Benign cephalic histiocytosis. Multiple brown papules on the face of a young child. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-69.** Xanthoma disseminatum. Sclerotic form of xanthoma disseminatum in a patient who developed multiple myeloma. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-68.** Multicentric reticulohistiocytosis. Grouped firm red-brown papules on the dorsal surface of the fingers, hand, and wrist in this 73-year-old African American woman. Courtesy, Susan D Laman, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**gammopathy** (e.g., MGUS, multiple myeloma, CLL, Waldenstrom disease; usually IgG, but can be IgA or IgM)

- Lipoproteins: transport plasma lipids to peripheral cells
  - Basic structure = inner core (triglycerides + cholesterol esters) + outer shell (phospholipids, free cholesterol and apoproteins (bind receptors and activating enzymes))
  - Exogenous and endogenous pathways of lipoprotein synthesis exist
  - Types of lipoproteins:
    - ◆ Chylomicrons: mainly exogenous production
      - Central core of mainly triglycerides; outer shell contains various apoproteins (B-48, E, A-I, A-II, and C-II)

Table 3-26. Monoclonal Gammopathies in Dermatology	
Disorder	Immunoglobulin Type
Plane xanthoma	IgG
Sweet's syndrome	IgA
Primary (AL) amyloidosis	IgG
Necrobiotic xanthogranuloma	IgGκ
Scleredema	IgGκ
Scleromyxedema	IgGλ
IgA pemphigus and subcorneal pustular dermatosis	IgA
Pyoderma gangrenosum	IgA
Erythema elevatum diutinum	IgA
POEMS syndrome	IgA and IgG
Schnitzler's syndrome	IgM
Cryoglobulinemia	Monoclonal IgM and IgG (type I) Monoclonal IgM + polyclonal IgG (type II) Polyclonal IgM and/or IgG (type III)
Waldenstrom's macroglobulinemia	IgM

- Becomes chylomicron remnant after most of the triglyceride content is hydrolyzed
- ◆ VLDL: mainly endogenous production in liver
  - Central core of mainly triglycerides; outer shell contains B-100, E and C-II
  - C-II needed for lipoprotein lipase activation
- ◆ IDL: remnant of VLDL after hydrolysis of most of triglycerides by lipoprotein lipase
- ◆ LDL: product of further triglyceride hydrolysis of IDL (now mainly cholesterol ester core and B-100 on surface)
  - Uptake into hepatocytes by apo B-100/E

**Table 3-27.** Important Hyperlipoproteinemias

Type	Pathogenesis	Laboratory Findings	Clinical Findings	
			Skin (types of xanthoma)	Systemic
Type I (familial LPL deficiency, familial hyperchylomicronemia)	Deficient or abnormal LPL Apo C-II deficiency  Deficient glycosyl-phosphatidylinositol-anchored HDL-binding protein	Slow chylomicron clearance Reduced LDL and HDL levels  Hypertriglyceridemia	<b>Eruptive</b>	No increased risk of coronary artery disease
Type II (familial hypercholesterolemia or familial defective apo B-100)	<b>LDL receptor defect</b> Reduced affinity of LDL for LDL receptor due to dysfunction of apo B-100 (ligand) Accelerated degradation of LDL receptor due to missense PCSK9 mutations* Defective LDL receptor adaptor protein 1 (required for receptor internalization)	Reduced LDL clearance <b>Hypercholesterolemia</b>  Hypertriglyceridemia	<b>Tendinous, tuberoeruptive, tuberous, plane (xanthelasma, intertriginous areas, interdigital web spaces<sup>†</sup>)</b>	<b>Atherosclerosis</b> of peripheral and coronary arteries
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apo E deficiency)	Hepatic remnant clearance impaired due to apo E abnormality; patients only express the apo E <sub>2</sub> isoform that interacts poorly with the apo E receptor	Elevated levels of chylomicron remnants and IDLs <b>Hypercholesterolemia</b> Hypertriglyceridemia	<b>Tuberoeruptive, tuberous, plane (palmar creases) – most characteristic</b> <b>Tendinous</b>	<b>Atherosclerosis</b> of peripheral and coronary arteries
Type IV (endogenous familial hypertriglyceridemia)	Elevated production of VLDL associated with glucose intolerance and hyperinsulinemia	Increased VLDLs Hypertriglyceridemia	<b>Eruptive</b>	Frequently associated with type 2 non-insulin-dependent diabetes mellitus, obesity, alcoholism
Type V	Elevated chylomicrons and VLDLs; subset related to apo A-V defect	Decreased LDLs and HDLs Hypertriglyceridemia	<b>Eruptive</b>	Diabetes mellitus

*Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very-low-density lipoprotein*  
<sup>\*</sup>Gain-of-function mutations cause autosomal dominant hypercholesterolemia<sup>4</sup>, whereas loss-of-function mutations (most prevalent in African-Americans) result in low LDL levels<sup>5</sup>.  
<sup>†</sup>Said to be pathognomonic for homozygous state.  
 (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- ◆ HDL: removes cholesterol from tissues
  - ➔ free cholesterol esterified by lecithin: cholesterol acyltransferase
  - ➔ Requires apoprotein A-I on HDL
- Hyperlipidemias have a variety of clinical findings (Table 3-27)

#### Cutaneous xanthoma types

- **Eruptive xanthomas**: numerous red-yellow papules on **extensor surfaces, buttocks**, intertriginous areas, and orally (Fig. 3-70)
  - Triglycerides usually >3000 mg/dL
  - Pathogenesis: may be primary or secondary
    - Primary: type I, IV, and V hyperlipidemias
    - Secondary: obesity, diabetes, alcohol abuse, medication-induced (**oral retinoids**, protease inhibitors, olanzapine, and estrogen replacement)
- **Tuberous xanthomas**: yellow-pink indurated nodules mainly on **elbows and knees**
  - Most strongly a/w type II and III
- **Tendinous xanthomas**: firm nodules on **Achilles tendon** and extensor tendons of fingers/hands that develop in third decade
  - Usually seen in type II hyperlipidemia (>type III)



**Figure 3-70.** Eruptive xanthomas due to hypertriglyceridemia. The lesions favored the extensor surface of the lower extremities, in particular the knees. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- **Plane xanthomas:** may be localized or diffuse
  - Occurrence on **palmar/finger creases** (xanthoma striatum palmare) nearly pathognomonic for **dysbetalipoproteinemia** (Fig. 3-71)
  - Occurrence in **intertriginous areas and web spaces of fingers** usually diagnostic of **homozygous familial hypercholesterolemia** (type II hyperlipidemia) (Fig. 3-72)



**Figure 3-71.** Xanthomas of palmar striae. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)



**Figure 3-72.** Plane xanthoma. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

- May occur in monoclonal gammopathy (plasma cell dyscrasia usually) with no lipid abnormalities; favors neck, upper trunk, intertriginous and periorcular areas
- **Xanthelasma** = plane xanthoma on eyelids
  - Only 50% have hyperlipidemia
  - Surgical treatment is best option
- **Verruciform xanthoma:**
  - Benign verrucous plaque(s) typically occurring in **mouth or genital area**
  - Often confused for warts clinically and histologically
  - Not a/w hyperlipidemia
  - May be a/w CHILD syndrome and any disorder that causes epidermal damage (epidermolysis bullosa, GVHD, LS&A, and pemphigus)
  - Unique histology: papillomatous epidermal hyperplasia w/ **foam cells in dermal papillae**

#### Pathology

- **Foam cells** (macrophages w/ lipidized cytoplasm) in dermis
  - Foam cells located more superficially in plane xanthomas, and deeper in dermis/SQ in tuberous and tendinous xanthomas

#### Treatment

- Determine underlying lipoprotein disorder and contributing factors, correct via various interventions (dietary modifications, lipid-lowering meds, surgical excision, and chemotherapy in certain monoclonal gammopathies)

### 3.9 URTICARIA AND ANGIOEDEMA

#### Urticaria

##### Epidemiology

- Up to 20% of population will have **acute urticaria** (duration <6 weeks),
  - 1% may develop into chronic urticaria (duration ≥6 weeks)
- F > M overall, and for chronic urticaria, dermatographism, and cold urticaria
  - M > F for delayed pressure urticaria

##### Pathogenesis

- Many cases of urticaria are idiopathic and causes vary (e.g., allergy, autoimmune, infections, and drugs)
- In **children, the most common cause is viral or idiopathic**, but other causes include:
  - Infectious (assess for symptoms of UTI, URI, or GI infection)
  - Allergic: foods, meds, and other environmental allergens
  - Physical stimuli: pressure, solar, cholinergic, and cold
  - Arthropod bite reactions ("papular urticaria")
  - Malignancy (most commonly lymphoma)



- Mast cell is the primary cell responsible for urticaria (though basophils and eosinophils play role)
  - Contains proinflammatory mediators:
    - Preformed: **histamine**, proteases, and heparin
    - Newly-formed: **prostaglandin D2**, **leukotrienes** C4/D4/E4, platelet-activating factor, and cytokines (TNF- $\alpha$ , IL-1, IL-4, IL-5, IL-6, and IL-8)
  - Degranulating stimuli → release of mediators by mast cells
    - **Immunologic mechanisms**: autoantibodies against Fc $\epsilon$ RI (seen in high % of chronic urticaria pts; occurs via autoimmune cross-linking of receptors) or IgE; IgE-dependent allergic response (e.g., to food, med, latex, or infection)
      - ◆ Drug-induced immunologic urticaria: PCN and cephalosporins (>TMP/SMX, and minocycline), latex gloves, or medical devices
    - **Non-immunologic mechanisms**: opiate-mediated release of mast cell contents, C5a anaphylatoxin, stem cell factor, neuropeptides (e.g., substance P and VIP)
- Other causes of urticaria include immune complex deposition (i.e., in urticarial vasculitis), vasoactive stimuli like **nettle**, aspirin/NSAIDs, **radiocontrast media**, **polymyxin B**, ACEI (due to ↑ **bradykinin**), and dietary pseudoallergens
  - **Aspirin** → exacerbation of chronic urticaria in 30%

#### Clinical features

- Characterized by **wheals**: swelling and erythema of skin from plasma leakage in superficial dermis
  - May have “**flare**” of **erythema** surrounding them
  - Intensely itchy
  - Individual lesions **last <24 hours**
- “Acute” vs “chronic” urticaria:
  - **Acute**:
    - Most common causes: **idiopathic (#1)** > **URIs (#2)** > **drugs ( $\beta$ -lactams most common)** and **foods**
    - Typically fast-onset (exception: drug-induced acute urticaria may start days after triggering agent)
  - **Chronic**:
    - Most common causes: “**ordinary**” (60%; consists of idiopathic and autoimmune autoantibodies against Fc $\epsilon$ RI or Fc portion of IgE, infection-related, and pseudoallergic) > **physical (35%)** > **vasculitic (5%)**
    - Autoimmune etiology in up to 50%
    - **a/w autoimmune thyroid disease**, vitiligo, IDDM, RA, *H. pylori* gastritis, and parasitic infections
    - Mean duration: 3–5 years
- **Physical urticaria**: induced by physical stimuli
  - **Dermatographism**: urticaria develops at sites of friction/scratching/stroking
    - Most common physical urticaria
    - Reproducible by scratching back – occurs seconds to minutes after provocation
    - Worse in evening
  - **Delayed pressure urticaria**: deep red swelling at anatomic areas of high friction/pressure (e.g., waistline after wearing tight-fitting clothes)
    - May be quite delayed, up to 12 hrs after stimulus
    - Painful, itchy, and possibly long lasting → ↓QoL
    - May be a/w arthralgias, malaise, and flu-like symptoms
- **Heat-induced**: very rare, urticaria after just a few minutes of heat contact
- **Cold urticaria**: rapid itch, erythema, and swelling after exposure; triggers include cold weather, air conditioners, and holding cold objects; “**ice cube**” test can aid in diagnosis (+ in PCCU, negative in reflex cold and familial cold urticaria); patients should **never swim alone** as massive mediator release can → hypotension
  - Primary cold contact urticaria (PCCU): usually idiopathic; young adults; acute or chronic; can have systemic symptoms like syncope; **positive ice cube test**
  - Secondary cold contact urticaria: may be due to cryoglobulinemia, cryofibrinogenemia, hepatitis B/C, lymphoproliferative disease, or mononucleosis)
  - Reflex cold urticaria: widespread urticaria after generalized cooling of body
  - Familial cold urticaria: (discussed in [Pediatric Dermatology](#) Chapter)
- **Cholinergic urticaria**: distinct lesions (multiple 2–3 mm slightly papular wheals with pronounced flare) occurring after sweating/↑ body temperature in young adults (e.g., after exercise, hot bath, and strong emotions)
  - May have systemic symptoms (e.g., faintness and wheezing) and be chronic
- **Adrenergic urticaria**: blanched vasoconstricted halos around pink wheal
  - Can reproduce lesions by intradermal norepinephrine injections
- **Solar urticaria**: discussed in [Physical Dermatoses](#) section
- **Aquagenic urticaria**: lesions similar to cholinergic, response to water exposure
  - Can be seen in cystic fibrosis
- **Urticarial vasculitis**: lesions that resemble urticaria but **last >24 h**, **burn/hurt** rather than itch and often **bruise**; histology shows mild LCV (+/– eosinophils)
  - Typically middle-aged women
  - Pain/burning > itch
  - Usually chronic
  - Angioedema in one third of patients
  - **Arthralgias (50%)**, GI involvement (20%), obstructive pulmonary dz (20%), and others (renal, ocular, cardiac, livedo, and intracranial HTN)
  - May be a/w **autoimmune CTDs** and infections
  - Can have ↑ESR, ↓complement, and (+)ANA
  - NSAIDs first line, but may need other agents (e.g., colchicine, dapsone, MTX, or steroids)
- **Schnitzler’s syndrome**: chronic **urticaria** (burn > itch), **fevers**, **bone pain**, arthralgia/arthritis, ↑ESR, and **IgM gammopathy**
  - Neutrophilic infiltrate on histopathology; **anakinra** is a good treatment

#### Histopathology

- Superficial dermal edema, vasodilation, scant perivascular and **interstitial infiltrate predominantly composed of neutrophils** (> eosinophils, lymphocytes)
  - Also see marginated neutrophils in vessel lumens
- Dermal neutrophilia seen 1 h into process



### Testing

- RAST and skin prick (intradermal) testing can help identify environmental allergens in acute urticaria
  - Most helpful to determine etiology of acute urticaria to foods, venom, and meds
  - RAST has 20% false-negative rate
- For recalcitrant chronic urticaria, consider CBC w/ differential, ESR/CRP, **thyroid antibodies**, thyroid function tests, anti-FcεRI and anti-IgE antibodies, immunoassays, functional assays (e.g., HRA), and autoreactivity (e.g., ASST)

### Treatment/clinical course

- Soothing lotions (e.g., containing pramoxine and/or menthol); avoidance of triggers (e.g., overheating, cold exposure, and vibratory stimuli)
- May need to **avoid aspirin**, NSAIDs, and opiates
- Exclusion diets/low pseudoallergen diets may be helpful in some cases
- **First line treatment = H1 antihistamines** (sedating and non-sedating); can consider adding H2 antihistamine
- For more recalcitrant cases, consider doxepin, short courses of systemic steroids, montelukast, phototherapy, sulfasalazine, cyclosporine, colchicine, dapsone, antimalarials, MMF, and omalizumab

## Angioedema

### Epidemiology

- Causes: Idiopathic (#1 cause), physical stimuli (temperature, vibration), Type I hypersensitivity rxns (drugs other than ACE-I, arthropod bites, food allergies), "pseudoallergic" (NSAIDs, ASA, IV contrast), C1 inhibitor deficiency syndromes (HAE, AAE), and ACE-I induced angioedema
- Hereditary angioedema (HAE) in 1:10,000-1:50,000; starts in first to second decade and more severe in adolescence
  - Type I HAE most common (80%–85% of HAE cases)
  - Gender predilections: types I and II (M = F); type III (F > M)
- Acquired angioedema (AAE) starts in middle age

### Pathogenesis

- Similar to urticaria for majority of cases with urticaria + angioedema; **for cases of angioedema LACKING urticaria (HAE, AAE) and ACE-I induced angioedema, excess bradykinin is the cause**
- Must rule out C1 esterase inhibitor (C1 inh) deficiency in cases of angioedema without urticaria
- **Hereditary angioedema (HAE):**
  - Types I and II due to **mutations in C1 inh** (type I has ↓C1 inh levels; type II has ↓C1 inh function)
  - Type III due to an activating mutation in Hageman factor (FXII)
  - All forms of HAE are **autosomal dominant**
- **Acquired angioedema (AAE):**
  - May be Type I (consumption of C1 inh) or Type II (inhibitory autoantibodies against C1 inh)
  - May be due to **B-cell lymphoproliferative disorders**, plasma cell dyscrasias, or **autoimmune CTDs**

- Acquired and hereditary forms result in **↑bradykinin** levels and **↓C4 levels (screening test of choice)**
  - **↓C1q levels** → seen in **acquired angioedema only!**
  - **C1 inh levels** → helps distinguish between types I and II HAE
    - **↓C1 inh** in Type I HAE
    - **Normal/↑ C1 inh** in type II
- **Drug-induced angioedema**
  - Most commonly **ACE inhibitors** (lisinopril, enalapril > captopril) occurs in 0.2% of all new users; **five-fold ↑risk in blacks**; 77% occur within first 3 weeks, almost all within first year; ACE inhibitors block kinase II → **↑bradykinin**
  - Others causes (NOT bradykinin-induced): PCN, cephalosporins, NSAIDs, radiocontrast media, and monoclonal antibodies (biologics)

### Clinical features

- Characterized by **deep swellings of skin/mucosa** (in deeper dermis and subcutaneous/submucosa)
  - Painful, non-erythematous
  - Non-pitting, non-pruritic (but may burn or cause pain)
  - **Commonly lasts 2–5 days** (worst in first 36 hours)
  - Face most commonly affected (**lips, eyelids, throat, ears, and nose**)
  - **May** → **anaphylaxis if throat involved** (laryngeal or epiglottic edema → stridor)
  - Associated symptoms: GI pain, N/V/diarrhea (edema of bowel wall), and urinary retention
  - Up to 50% of pts w/chronic urticaria will also have angioedema at some point; however, if see angioedema in absence of urticaria, must consider HAE and AAE!
- Vibratory angioedema: vibration → localized swelling lasting about half an hour
  - Causes include running and operating machinery (e.g., lawnmower)
  - Familial form has systemic symptoms
- HAE:
  - Type I and II: estrogens and trauma can → attacks
    - Episodes last 2–3 days
    - Avoid ACEI (can trigger attacks)
  - Type III: later age of onset (in teens), **↑facial edema**

### Diagnosis

- If HAE or AAE are suspected, check C4, C1 inh (quantification and function), and C1q

### Treatment/clinical course

- Similar to treatments for urticaria
- Intensive support (e.g., intubation and tracheostomy) may be needed
- Should carry epi-pen in case of angioedema in oropharynx
- For **C1 inh deficiency**, oral **danazol** is ToC for prophylaxis, and **C1 inh concentrate** is ToC for acute attacks
  - Danazol and C1 inh concentrate can be used prophylactically prior to surgical procedures
  - A newer option is icatibant, a synthetic bradykinin B2 receptor antagonist
- **Anaphylaxis:** life-threatening reaction to drugs that p/w both skin (urticaria/angioedema) and systemic

(hypotension and tachycardia) findings; occurs **within minutes of parenteral** (> oral) administration of drugs; most common drugs: **PCN** (1/5000 patients), **latex** (especially mucosal contact), topical antibiotic use (**bacitracin**, Neosporin, and rifamycin); and radiocontrast media (anaphylactoid); Rx: hospitalization for serious cases + systemic steroids + sub-Q epinephrine

### 3.10 NEUTROPHILIC DERMATOSES

#### Sweet's syndrome (acute febrile neutrophilic dermatosis)

##### Epidemiology

- Usually middle-aged
- **F > M (3:1 for classic Sweet's)**
  - M = F for cancer-associated Sweet's
- Five major subtypes: classic (60%–70%), cancer-associated (10%–20%), inflammatory disease-related (10%–15%), drug-induced (5%), and pregnancy (2%)

##### Pathogenesis

- Unknown; may have (+) pathergy

##### Clinical features

- **Tender/burning**, red, well demarcated, expanding, **edematous/"juicy"** papules/plaques ([Fig. 3-73](#))
  - Favors **head/neck and upper extremities**
  - Rapid onset
  - May become vesiculobullous or pustular, and may have a targetoid appearance
  - In drug-induced Sweet's, lesions occur 1 to 2 weeks after drug administration
  - **Ulcerative, bullous and oral lesions** → stronger a/w hematologic disorders/malignancy
- Extracutaneous features: **fever** (50%–80%), malaise, preceding URI or flu-like symptoms, **leukocytosis** (70%), **arthralgias/arthritis**, **ocular involvement** (conjunctivitis, episcleritis, and iridocyclitis)



**Figure 3-73.** Sweet's syndrome. Markedly edematous lesions on the upper back. Courtesy, Kalman Watsky, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Lab abnormalities:
  - ↑ESR/CRP (90%)
  - Leukocytosis: neutrophilia w/ ↑band forms ("left shift")
- Various triggers:
  - Infections: mainly **streptococcus** and yersiniosis
  - Cancer: especially **AML**, but also other hematologic and solid malignancies
  - **IBD**
  - Drugs: **G-CSF**, **GM-CSF**, **ATRA**, **TMP/SMX**, **minocycline**, **OCPs**, furosemide, and hydralazine
  - Other: autoimmune CTDs, **pregnancy**, **HIV**, and **Hep C**

##### Histopathology

- **Diffuse dermal neutrophilic infiltrate w/ karyorrhexis + massive papillary dermal edema**
  - Generally **lacks LCV** (although some "bystander" damage is done to vessels within inflammatory soup)
  - Massive papillary dermal edema is responsible for "pseudovesicular" clinical morphology
- Variants:
  - **Subcutaneous Sweet's**: neutrophils involve subcutis in a lobular pattern; p/w deep-seated red nodules on extremities
  - **Histiocytoid Sweet's (variant)**: dermal and/or SQ infiltrate of neutrophils and "histiocytoid" cells (immature myeloid cells that stain positively for myeloperoxidase); recent studies suggest that this form may have a stronger association w/ hematologic malignancy

##### Treatment/clinical course

- Resolves within 2–3 months without scarring (vs PG)
- Can recur in up to one third of patients
- **ToC = systemic steroids** (prednisone 0.5–1.0 mg/kg daily for 4–6 weeks; **WORKS FAST!**)
  - Others: SSKI, dapsone, and colchicine

##### Additional boards factoids

- Marshall syndrome: rare childhood disease that has Sweet's-like lesions that resolve w/ acquired cutis laxa at affected sites

#### Neutrophilic dermatosis of the dorsal hands

- Features of PG + Sweet's
- Ulcerative red-violaceous plaques on dorsal hands ([Fig. 3-74](#))
- Rx: prednisone, dapsone

#### Pyoderma gangrenosum (PG)

##### Epidemiology

- Adults (20–60 yo); **F > M**
- Half have associated with a systemic inflammatory disorder (**IBD** most common, up to 30%), hematologic disorder (e.g., **IgA monoclonal gammopathy**, **AML**, **CML**, hairy cell leukemia, and polycythemia vera), or inflammatory arthritis



**Figure 3-74.** Neutrophilic dermatosis of the dorsal hands. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

### Pathogenesis

- Likely immunologic disorder
- Genetic: some cases are caused by a mutation in CD2-binding protein 1 (PAPA syndrome)
- **Pathergy** (30%): may initiate and/or aggravate disease

### Clinical features

- Major types include classic (ulcerative), bullous (less destructive than ulcerative type; strongly associated with myeloproliferative disorders), pustular, and superficial granulomatous (aka vegetative; cribriform superficial ulcers on trunk)
- **Classic (ulcerative) PG**
  - Starts as inflamed papulopustule/bulla → **painful** undermining ulcer w/ **overhanging, irregular, violaceous border** and purulent/vegetative base; **satellite lesions** arise at periphery of ulcer → break down and fuse with central ulcer
    - Heals with atrophic **cribriform scar**
    - Most commonly on lower extremities (pretibial)
  - Related variants:
    - Pyostomatitis vegetans: chronic vegetative pyoderma of oral mucosa associated with IBD
    - Peristomal PG: painful, undermined lesions around ostomy; associated with IBD
    - **Classic PG in kids (rare)**: most common on head and anogenital region; usually associated with IBD or leukemia
- **Pustular PG**
  - **Multiple small pustules** that do not progress to ulcers
  - associated with IBD in most cases
- **Bullous PG**
  - More superficial, less destructive than classic PG
  - More widespread distribution (face, dorsal hands) → overlaps with bullous Sweet's disease
  - More strongly associated with **hematologic malignancy** (AML, CML, MDS, P. vera)
- **Vegetative PG**
  - Least aggressive form
  - associated with superficial, **painless cribriform ulcers** on trunk; responds well to conservative treatment
  - Usually arises as result of trauma (e.g., surgery)
  - Not associated with underlying systemic diseases

### Histopathology

- Epidermal ulceration with dense underlying **superficial and deep dermal neutrophilic infiltrate** (inflammation deeper than Sweet's), leukocytoclasia, epidermal pustules, and dermal edema
  - Neutrophilic infiltrate extends laterally beyond overlying ulcer ("undermining infiltrate")
- PG is a diagnosis of exclusion!!!
  - Histologic features are not entirely specific
  - **Must rule out infection, vasculitis, vasculopathy, and malignancy**

### Treatment/clinical course

- Course varies depending on type of PG
- Good wound care is essential for all patients
- Must search for underlying diseases
  - GI: colonoscopy, stool studies
  - Heme: CBC, peripheral smear, SPEP, +/- bone marrow biopsy
- Treatment:
  - Initial: topical, intralesional steroids (mild disease); systemic steroids (1 mg/kg per day) if more severe
  - Recalcitrant/very severe disease: **infliximab and cyclosporine** are ToC; may try other immunosuppressives if this fails

## Behcet's disease

### Epidemiology

- Japanese, Middle Eastern, and Mediterranean (highest prevalence in Turkey)
- Usually 20–35 yo
- M > F
- May be familial in subset of cases

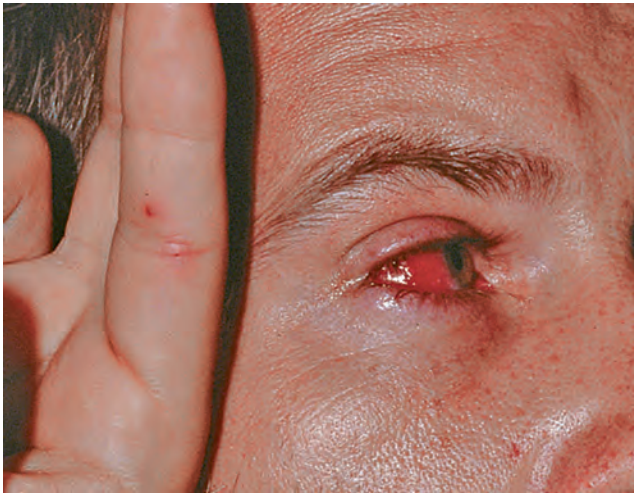
### Pathogenesis

- Multifactorial; circulating immune complexes and neutrophil dysregulation → vascular injury
- Strongly associated with **HLA-B51 allele**

### Clinical features

- Recurrent oral ulcerations (**aphthous stomatitis = first and most common symptom**) at least three times in a year + two of the following:
  - **Recurrent genital ulceration**: large, irregular aphthae on scrotum, penis, and vulva
  - **Ocular lesions**: uveitis (posterior > anterior), conjunctivitis, iridocyclitis, and retinal vasculitis (may → blindness)
  - Cutaneous lesions (**facial/acral papulopustules** (Fig. 3-75)), purpura, EN-like lesions on legs/buttocks, and positive pathergy test
    - **Pathergy test**: needle stick or intradermal injection of saline → papulopustule at site of trauma within 24–48 hrs
- Of note, oral ulcerations can occur anywhere in oral cavity/lips, be single or multiple, large in diameter, and have a gray base with surrounding erythema
- Can affect all organs with unpredictable course:
  - Ocular (90%)
    - **#1 cause of morbidity**, including blindness





**Figure 3-75.** Behçet's disease: systemic involvement. Iritis and cutaneous pustular vasculitis. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Vascular: superficial migratory thrombophlebitis (30%) and less frequently SVC thrombosis
- Other: joints (50% develop arthritis), neurologic (meningoencephalitis, MS-like symptoms), cardiopulmonary, renal (glomerulonephritis), and GI

#### Histopathology

- Classically neutrophilic infiltrate around vessels w/ leukocytoclastic vasculitis
  - Lymphocytic vasculitis may be seen in older lesions

#### Treatment/clinical course

- Important to treat because of systemic involvement, but difficult to control (no ToC exists)
  - Options: colchicine, dapsone, thalidomide, IFN- $\alpha$ -2a, MTX, TNF- $\alpha$  inhibitors, and azathioprine
- Symptomatic relief (e.g., mild mouthwashes and sucralfate suspension) important

#### Additional boards factoids

- MAGIC syndrome = features of Behçet's and relapsing pychondritis

### Bowel-associated dermatosis arthritis syndrome (bowel bypass syndrome)

#### Epidemiology/pathogenesis

- Classically pts with jejunoileal bypass surgery and blind loops of bowel
  - Occurs 1–6 years after bowel surgery
  - Other causes: biliopancreatic diversion, gastric resection, IBD, PUD, and diverticulitis
- Bacteria in blind loop of bowel → immune complexes w/ bacterial antigens are deposited in skin/synovium

#### Clinical features

- Constitutional and serum-sickness like symptoms (e.g., malaise, fever, chills, arthralgias/myalgias) usually precede rash

- Classic rash = red to purpuric papulopustules over proximal extremities and trunk
  - May also have **tender SQ nodules** (trunk, extremities; due to lobular panniculitis; heals w/ depressed scars) or **EN-like lesions** (lower legs; non-scarring)
- Diarrhea/malabsorption, hepatic failure, kidney stones, and gallstones

#### Histopathology

- Classic papulopustules: nodular or perivascular dermal neutrophilic inflammation
- Tender, scarring SQ nodules: lobular neutrophilic panniculitis (→ loss of fat lobules and scar)
- EN-like lesions: resembles EN

#### Treatment/clinical course

- Skin lesions may last up to 1 month and recur frequently
- Antibiotics and immunosuppressive agents → temporary improvement
- Surgical correction of blind bowel loop or revision of bypass is curative

## 3.11 EOSINOPHILIC DISORDERS

- Various disorders can have significant numbers of eosinophils histologically, including: arthropod bites, urticaria, allergic contact and atopic dermatitis, drug reactions, and autoimmune blistering disorders (e.g., BP, PV, inflammatory EBA)

### Granuloma faciale

- Discussed in [Vasculitides and Vasculopathies](#) section

### Eosinophilic folliculitis

- Discussed in [Follicular and Eccrine/Apocrine Disorders](#) section

### Papuloerythroderma of Ofuji

- Elderly Japanese men most commonly
- Generalized pruritic red-brown papules → erythroderma sparing skin folds ("deck chair sign")
- Eosinophilia, lymphopenia,  $\uparrow$ IgE, lymphadenopathy common; sometimes a/w gastric carcinoma, B-cell lymphoma, and T-cell lymphoma
- Chronic but responsive to systemic steroids (TOC), PUVA, and oral retinoids

### Wells' syndrome (eosinophilic cellulitis)

- Unknown etiology, but can be triggered by myeloproliferative diseases, infections, drugs, arthropod bites, and Churg-Strauss syndrome
- Recurrent tender/itchy erythematous indurated cellulitis-like plaques (occasionally arcuate)
  - Extremities > trunk
  - Malaise and eosinophilia typically present
  - Lesions resolve over 1–2 months



- Histology: striking eosinophilic infiltrate in interstitial dermis w/ classic “**flame figures**”
  - Flame figures = collagen fibers coated with eosinophil granule proteins (most importantly, **major basic protein**)
- Systemic steroids are ToC → quick improvement

## Hypereosinophilic syndrome (HES)

- Criteria:
  - Peripheral blood eosinophil counts  $>1500/\text{mm}^3$  for  $\geq 6$  months (or  $<6$  months + organ damage)
  - No evidence of infectious, allergic, or other underlying causes
  - Symptoms/signs of end-organ involvement
- Mucocutaneous lesions ( $>50\%$ )
  - Most commonly p/w **itchy red papules/nodules**, urticaria, angioedema,
  - Mucosal ulcers (a/w myeloproliferative HES and more aggressive course)
- Systemic symptoms: fever, cough, malaise, and myalgias
- **#1 cause of death = congestive heart failure** (5 year survival = 80%)
- Successful treatment correlates with decreasing eosinophil count (1000–2000 mc)
- Two major subtypes of HES:
  - Myeloproliferative HES
    - Most commonly **FIP1L1-PDGFR** fusion gene → constitutively activated tyrosine kinase
    - May have  $\uparrow$  serum tryptase and vitamin B12, **endomyocardial fibrosis/cardiomyopathy**, hepatosplenomegaly, CD25+ atypical mast cells on bone marrow biopsies, and constitutional symptoms (on presentation)
    - Treatments include **imatinib** (if fusion gene present), prednisone, hydroxyurea, interferon, and mepolizumab/reslizumab (anti-IL-5 antibodies)
  - Lymphocytic HES
    - **Clonal T-cell proliferation** ( $\uparrow$ Th2 cytokines, especially IL-5 → eosinophil activation)
    - Itch/eczema/erythroderma/angioedema/urticaria w/  $\uparrow$ IgE, eosinophilia, and lymphadenopathy
    - Generally **benign course** (when compared to myeloproliferative HES):
      - ◆ Rarely develop cardiac complications
      - ◆ However, there is  $\uparrow$ risk of T-cell lymphoma
    - Treatment: **prednisone (first line)**, interferon, and mepolizumab/reslizumab

infections, other fungi, viruses, and parasites), drug, pregnancy, and neoplasms (usually lymphoproliferative malignancies)

### Clinical features

- Start as firm pink papule → erythematous annular lesions that **migrate centrifugally** (outward; up to 6 cm diameter in 2 weeks)
- **Trailing scale** (inner margin desquamation) is common in superficial lesions, but not deep lesions
- Most commonly on thighs/hips, but can become more generalized

### Histopathology

- Superficial EAC: mild spongiosis, focal parakeratosis, and perivascular lymphohistiocytic infiltration, which is tight and dense (“**coat sleeve**”)
- Deep EAC: deep and tight perivascular lymphohistiocytic inflammation

### Treatment

- Treat underlying disorder if present; otherwise topical steroids

### Prognosis/clinical course

- Lesions last days to months

## Erythema marginatum

### Epidemiology

- Primarily seen in children 5–15 yo who are NOT treated for **group A  $\beta$ -hemolytic Streptococcus** infections of pharynx ( $\approx 3\%$  of untreated pts)
- More prevalent in underdeveloped countries

### Pathogenesis

- Seen in setting of **rheumatic fever** (aberrant humoral/cellular immune response to group A  $\beta$ -hemolytic strep infection; may be related to cross-reacting epitopes)
  - Rheumatic fever: starts 2–5 weeks after infection; two major or one major + two minor criteria, in addition to evidence of group A strep infection (culture, anti-DNase B titer, and antistreptolysin O)
    - Jones major criteria: carditis, migratory polyarthritides, **erythema marginatum**, subcutaneous nodules, or Sydenham’s chorea
    - Jones minor criteria: fever, arthralgias, or abnormal laboratory findings ( $\uparrow$ ESR,  $\uparrow$ CRP, and  $\uparrow$ PR interval)

### Clinical features

- Migratory expanding annular/polycyclic patches/plaques starting as macules
  - Can migrate 2–12 mm in half day
  - Usually trunk, axillae, and proximal extremities
- Typically resolves in a few weeks and is seen in active phase of rheumatic fever (in conjunction w/ carditis)

### Treatment/clinical course

- No treatment shown to alter natural disease course

## 3.12 FIGURATE ERYTHEMAS

### Erythema annulare centrifugum (EAC)

#### Epidemiology

- Peaks in fifth decade

#### Pathogenesis

- Unknown, but may be an immune reaction to an antigen such as infection (e.g., **tinea pedis**, other dermatophyte

## Erythema migrans

### Epidemiology

- Most commonly seen in US (southern New England, SE NY, NJ, eastern PA, eastern MD, Delaware, and certain parts of MN/WI/MI) and Europe (particularly central Europe)
- White-footed mice and **white-tailed deer** are natural hosts for *Borrelia*

### Pathogenesis

- Due to *Borrelia burgdorferi* (a spirochete) that is inoculated by *Ixodes* tick bites
  - Note: these ticks can also transmit babesiosis and human granulocytic anaplasmosis
- Tick **MUST be attached for >1 day** (and usually >48 hrs) to transmit disease

### Clinical features

- **Large annular red expanding patch (≥5 cm)** at site of *Borrelia*-infected tick bite 7–15 days after tick detachment
  - Trunk and intertriginous areas
  - Initial manifestation of Lyme disease (up to 90% of infected patients have *E. migrans*)
  - Smaller secondary lesions possibly due to lymphatic/hematologic spread or multiple tick bites
- Lyme disease has different symptoms in various phases
  - Early localized disease: flu-like symptoms and lymphadenopathy
  - Early disseminated disease: **Bell's palsy**, arthralgias, **AV block**, and iritis
  - Chronic disease: chronic arthritis (usually monoarticular of large joints), encephalopathy, and acrodermatitis chronica atrophicans (chronic sclerosing dermatitis)

### Laboratory testing

- Confirmed diagnosis requires erythema migrans + either known exposure or laboratory evidence of exposure (positive tissue/fluid culture, tissue/fluid PCR, and anti-*Borrelia* antibodies via ELISA and Western blot – **peak IgM response occurs 3–6 weeks into infection**)

### Treatment

- Depends on stage of disease, age, and pregnancy status
- Typically **doxycycline** in early localized disease and mild early disseminated or chronic disease for non-pregnant adults and children ≥8 years (**amoxicillin** in children <8 years or pregnant women)
- Ceftriaxone is best IV treatment (usually for Lyme meningitis)

### Prognosis/clinical course

- If left untreated:
  - *E. migrans* lesions self-resolve in 6 weeks
  - 60% develop arthritis (usually knee)

- 10% develop neurologic issues (usually Bell's palsy)
- 5% develop cardiac issues (usually AV block)

### Additional boards factoids

- Read Lyme Disease CME review Part I and II published in JAAD 2011 by Bhate and Schwartz for more info
- Agar for *Borrelia* = Barbour-Stoenner-Kelly medium

## Erythema gyratum repens

- **Paraneoplastic disorder** likely due to immune reaction against tumor-associated antigens, and subsequently cutaneous antigens (due to similarities/cross-reaction between tumor-associated antigen and cutaneous antigens)
  - Most common malignancies: **lung (most common) > breast and GI** (esp. esophagus/stomach)
- Multiple lesions w/ **"wood grain"** (polycyclic and serpiginous) appearance of erythema in concentric rings (**Fig. 3-76**); **rapid expansion (1 cm/day)** with itch and trailing scale; hands and feet are spared
- M > F
- Lesions resolve when neoplasm treated; lesions develop 1 year pre- to 1 year post-cancer diagnosis

### Flushing

- Not a figurate erythema, but still an erythema (change in skin color due to dilation of blood vessels in dermis)
- Wide differential (**Box 3-6**), which includes common and serious medical issues, as well as meds and alcohol use



**Figure 3-76.** Erythematous gyratum repens. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

**Box 3-6. Differential Diagnosis of Flushing****Common Causes**

- Benign cutaneous flushing
  - Emotion
  - Temperature
  - Food or beverage
- Rosacea
- Climacteric flushing
- Fever
- Alcohol

**Uncommon, Serious Causes**

- Carcinoid
- Pheochromocytoma
- Mastocytosis
- Anaphylaxis

**Other Causes**

- Medullary thyroid carcinoma
- Pancreatic cell tumor (VIP tumor)
- Renal cell carcinoma
- Fish ingestion
  - Histamine
  - Ciguatera
- Psychiatric or anxiety disorders
- Idiopathic flushing
- Neurologic
  - Parkinson's
  - Migraine
  - Multiple sclerosis
  - Trigeminal nerve damage
  - Horner syndrome
  - Frey syndrome
  - Autonomic epilepsy
  - Autonomic hyperreflexia
  - Orthostatic hypotension
  - Streeten syndrome
- Medications (see Table IV)

**Very Rare Causes**

Sarcoid, mitral stenosis, dumping syndrome, male androgen deficiency, arsenic intoxication, POEMS syndrome, basophilic granulocytic leukemia, bronchogenic carcinoma, malignant histiocytoma, malignant neuroblastoma, malignant ganglioneuroma, peri-aortic surgery, Lehigh syndrome, Roving syndrome

(From Leonid Izikson, Joseph C. English III, Matthew J. Zirwas. *Journal of the American Academy of Dermatology*. Volume 55, Issue 2, pp. 193-208. Elsevier. 2006)

### 3.13 FOLLICULAR AND ECCRINE/APOCRINE DISORDERS

#### Acne vulgaris

##### Epidemiology

- Peaks in adolescence; affects 85% between 11–30 yo

##### Pathogenesis

- Disease of pilosebaceous unit with multifactorial pathogenesis: *Propionibacterium acnes*, sebum overproduction, abnormal keratinization, and/or inflammation
- **Abnormal follicular keratinization** and formation of microcomedo → comedo rupture → release of keratin and sebum → inflammatory papule/pustule → nodule/cyst
- Hormones
  - Androgens (especially dihydrotestosterone (DHT) and testosterone) → ↑growth of sebaceous glands/↑sebum production
    - Androgen receptors are found on basal layer of sebaceous glands and outer root sheath of hair follicle
    - ↑androgen levels present during first 6 months and at adrenarche (DHEAS levels ↑)
- *Propionibacterium acnes*
  - G+ anaerobic rod
  - Produces lipases that break down triglycerides in sebum into FFAs, which are comedogenic and proinflammatory
  - Activates TLR-2 on macrophages, which induces proinflammatory cytokines (IL-1, IL-8, IL-12, and TNF-α) and attracts neutrophils
  - Produces **coproporphyrin III**, which fluoresces under Wood's lamp
- Dietary
  - Unclear, but skim milk, whey protein, and **high glycemic load** may contribute to acne

##### Clinical features

- Most common sites (sebaceous areas): face, neck, behind ears, upper trunk, and upper arms
- Frequently start as open and closed comedones
- May develop more inflammatory lesions including papules, pustules, nodules, and cysts; nodulocystic lesions can coalesce into plaques and sinus tracts
- As lesions resolve may leave post-inflammatory hyperpigmentation/erythema or scars (icepick, rolling, boxcar, anetoderma-like, hypertrophic, and keloidal)
- Women may **flare week prior to menstruation**

##### Histopathology

- Follicle filled with laminated keratin and debris, ± suppurative inflammation

##### Treatment/clinical course

- See Table 3-28 for treatment approach to acne
- Topicals: **retinoids**, **benzoyl peroxide**, azelaic acid, clindamycin, dapson, erythromycin, sodium sulfacetamide/sulfur, salicylic acid, chemical peels, and light/laser therapy
- Orals: oral antibiotics (TCNs, penicillins, sulfonamides, and erythromycin), hormonal agents (**spironolactone**, OCPs), **isotretinoin**, and prednisone
- Intralesional corticosteroids
- Multiple modalities for scarring, including laser resurfacing, subcision, dermabrasion, and fillers

**Table 3-28.** Treatment approach for acne

	Topical Retinoid	Topical Benzoyl Peroxide	Topical Benzoyl Peroxide + Topical Antibiotic	Systemic Antibiotic	Hormonal Therapy (Females Only)	Isotretinoin
<b>Acne type and severity</b>						
Comedonal	✓	✓	✓	✗	✗	✗
<b>Inflammatory</b>						
Mild	✓	✓	✓	✗	✗	✗
Moderate	✓	✓	✓	✓	✓	✗
Severe	✓	✓	✓	✓	✓	✓
Nodulocystic	✗	✗	✗	✓	✓	✓

### Additional boards factoids

- Topical retinoids downregulate TLR-2 expression
- Spironolactone has FDA black box warning for pts w/ history of breast cancer

## Acne variants

### Acne fulminans

- Males 13–16 yo
- May occur after isotretinoin initiation or dose increase
- Most severe cystic acne, w/ **systemic manifestations**
  - Acute suppurative nodules and plaques
  - Lesions are friable w/ **hemorrhagic crust**; can ulcerate and form black eschar
  - Often scars
  - Chest, shoulders, and back; rarely on face
  - Fever, ↑WBC, and ↑ESR
  - **Sterile osteolytic bone lesions** (sternum, clavicle, and long bones), arthralgias, myalgias, and hepatosplenomegaly can also be seen
- **Treat w/ oral corticosteroids, followed by oral isotretinoin** when acute inflammation has subsided
  - If a patient on isotretinoin develops acne fulminans → ↓isotretinoin dose immediately
- Polymorphisms in TLR-4 may be protective against acne fulminans

### Acne conglobata

- M ≫ F
- Severe eruptive nodulocystic acne, **without systemic manifestations** (vs acne fulminans)
  - Cysts, nodules, and large abscesses with sinus formation
  - **Suppuration is characteristic** (lesions contain thick, yellow, blood-tinged fluid)
  - **Secondary comedones** can be white, firm, cyst-like or polyporous (clusters of blackheads)
  - Often scars
  - Usually on trunk (especially the back); less severe on face
- Treat with isotretinoin; may need to pretreat with prednisone

### Solid facial edema in acne

- Swelling in midline face and cheeks
- Woody non-pitting, non-scaling induration (*peau d'orange* appearance)
- Acne predates edema by 2–5 years
- ToC = isotretinoin +/- ketotifen (antihistamine)
  - May also try prednisone, but not as successful

### Acne mechanica

- Repeated pressure/friction → obstruction of pilosebaceous unit (helmets, backpacks, collars, and fiddler's neck)
- Unusual distribution pattern based on external provoking factor

### Acne excoriée (de jeunes filles)

- Young women; may be a/w **underlying depression or anxiety disorder, OCD, body dysmorphic disorder, eating disorder, trichotillomania, or borderline personality disorder**
- **Self-mutilation** of imagined acneiform lesions or mild acne lesions → excoriated crusted erosions
- Treatment: antidepressants, behavioral modification, and psychotherapy

### Neonatal acne

#### Epidemiology

- Appears within first few weeks, resolves by 3 months
- 20% of healthy newborns
- M > F

#### Pathogenesis

- KOH may demonstrate *Malassezia* (subtype of neonatal acne, termed **neonatal cephalic pustulosis**)
  - Treatment: ketoconazole cream
- Other cases likely related to stimulation of sebaceous glands by **maternal androgens or transient androgen production**

#### Clinical features

- Cheeks and **nasal bridge** are common sites, but lesions may occur anywhere on the face/head/neck
- Inflammatory papules and pustules more common than comedones



### *Treatment/clinical course*

- Usually regresses over few months
- If mild, cleanse with gentle soap and water
- Topical retinoid, topical antibiotic, or benzoyl peroxide
- Oral antibiotics (erythromycin) or isotretinoin if severe

### *Additional boards factoid*

- Some neonates with trisomy 21 may develop a leukemoid reaction, which manifests as severe pustular eruption on the face, mimicking neonatal acne

## Infantile acne

### *Epidemiology*

- Appears around 3–6 months; usually resolves by 2–3 years
- M > F

### *Pathogenesis*

- Hormonal imbalance (hyperandrogenism)

### *Clinical features*

- More severe and persistent compared with neonatal acne
- Comedones (primarily) and inflammatory lesions including occasionally deep cysts
- Can result in **scarring**
- Usually limited to face

### *Treatment/clinical course*

- Therapy is often necessary due to risk of scarring
- Same options as neonatal acne
- If acne arises between ages 1–7 (mid-childhood acne) and signs of pubertal development are noted (pubarche, thelarche, etc) an endocrinology evaluation should be considered along with the following laboratory analysis: DHEAS, androstenedione, 17-OH-progesterone, and bone age
- May predict propensity towards future acne

## Transverse nasal crease

- Arise during early childhood
- Horizontal anatomical demarcation line at border of middle and lower third of the nose at junction of triangular and alar cartilage
- May contain milia/cysts/comedones

## Acne in setting of endocrinologic abnormality

### *Epidemiology/pathogenesis*

- Hyperandrogenism due to:
  - Polycystic ovarian syndrome (PCOS), suspect in females with hirsutism or irregular menses; most common endocrinopathy a/w acne
  - Congenital adrenal hyperplasia (children with acne)
  - Androgen-secreting tumors and Cushing's syndrome

### *Clinical features*

- Distribution depends on underlying cause of androgen excess
- **Adult women** may have acne along jawline or lower face

### *Workup*

- Initial workup: total/free testosterone, DHEAS, LH, and FSH (can also consider SHBG, 17-hydroxyprogesterone, prolactin, morning cortisol, and ACTH stimulation test)
  - ↑total testosterone → indicates **ovarian source**
    - PCOS has ↑testosterone and ↑LH/FSH ratio
    - Ovarian tumors have total testosterone levels >200 ng/dL
  - ↑DHEAS or ↑17-hydroxyprogesterone → indicates **adrenal source**
    - Congenital adrenal hyperplasia (defects in 21-hydroxylase or 11-hydroxylase); cortisol deficiency leads to over secretion of ACTH and overstimulation of adrenals → androgen excess
    - Adrenal tumors have DHEAS >8000 ng/mL

### *Treatment/clinical course*

- Treat underlying abnormality
- OCPs or spironolactone

### *Additional boards factoid*

- XYY genotype may have more severe acne

## Acne cosmetica

- Frequent/heavy use of cosmetics containing lanolin, petrolatum, vegetable oils, butyl stearate, isopropyl myristate, sodium lauryl sulfate, lauryl alcohol, or oleic acid → small closed comedones, small papules and pustules

## Pomade acne

- More common in **African Americans** using greasy/oily grooming substances on the scalp
- Closely set, monomorphic, small closed comedones on forehead and temples

## Chloracne

- Type of occupational acne caused by exposure to **chlorinated aromatic hydrocarbons** (found in electrical conductors, insulators, and insecticides/fungicides/herbicides)
  - **Agent orange** was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (**dioxin**), a chlorinated hydrocarbon
- Acne develops after several weeks of exposure
- May have recurrent outbreaks for many years after exposure
- Preferred sites are face, neck (including **retroauricular**), **axilla**, **scrotum**, and penis
- Treatment difficult; **ToC is isotretinoin** (high dose followed by low dose maintenance), topical retinoids, and surgical intervention for large lesions can be used

## Radiation acne

- Ionizing rays induce epithelial metaplasia in follicles → hyperkeratotic plugs
- Comedo-like papules in areas of previous radiation exposure
- Appears as the acute phase of radiation dermatitis resolves

## Acneiform eruptions

### Drug-induced acne

#### Epidemiology/pathogenesis

- a/w multiple meds:
  - Anabolic steroids
  - Androgens (testosterone)
  - Corticosteroids
  - **Halogens** (iodides and bromides)
  - Isoniazid
  - OCPs (containing androgen-like progestins)
  - Lithium
  - Phenytoin
  - Vitamins B2, B6, and B12
  - **EGFR inhibitors** (monoclonal antibodies: cetuximab and panitumumab; tyrosine kinase inhibitors: gefitinib, erlotinib, and lapatinib)
  - Other chemotherapy a/w acneiform eruptions:
    - mTOR inhibitors (sirolimus and tacrolimus)
    - Multikinase inhibitors (sunitinib and sorafenib)
    - MEK inhibitors (trametinib)
- **Mnemonic: "SHIELD yourself from acne with vitamin T:"** Steroids (anabolic, corticosteroids), **H**alogens, Isoniazid, EGFR inhibitors, Lithium, Dilantin (phenytoin), **V**itamin B2, B6, B12, Testosterone

#### Clinical features

- Abrupt-onset monomorphous inflammatory papules or pustules (classic in corticosteroid-induced acne)
- Usually **lacks comedones**
- Trunk > face
- In setting of **EGFR inhibitors**: occurs in usual acne-prone areas and sun-exposed areas, starts 1–3 weeks after beginning treatment, severity of reaction positively correlates with clinical response to medication; occurs in >80% of patients

#### Treatment/clinical course

- Discontinue offending med if possible
- For EGFR inhibitors: prophylaxis with doxycycline or minocycline started on same day as EGFR inhibitor therapy; also **do not use irritating agents like topical retinoids or benzoyl peroxide**

## Acne associated syndromes

### SAPHO (chronic recurrent multifocal osteomyelitis)

- Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis
- Affects children and young adults (usually appears in third decade); more common in Japan

- Inflammatory disorder of unclear etiology
- Characterized by RF(–) osteoarthropathy with various skin manifestations of varying degrees
- Bone disease precedes skin disease in the majority
- **Sternoclavicular area** is the most common site of inflammation
- Chest wall and mandible are most common areas of musculoskeletal pain
- Acne varies from mild to acne conglobata/fulminans; hidradenitis suppurativa and dissecting cellulitis can also be seen
- Pustulosis includes palmoplantar pustulosis and pustular psoriasis (psoriasis vulgaris can also be seen)
- a/w IBD
- Treatment: bisphosphonates, TNF- $\alpha$  inhibitors, MTX, NSAIDs, corticosteroids, colchicine, and anakinra
- Of note, "bull's head" sign may be seen on X-ray

## PAPA

- Pyogenic Arthritis (sterile), Pyoderma gangrenosum, Acne conglobata
- AD mutation in CD2 binding protein 1 (CD2BP1; aka PSTPIP1)
  - Part of autoinflammatory disease group as CD2BP1 interacts with pyrin (mutation → unopposed inflammation)
- Treatment: systemic or local corticosteroids, dapsone, infliximab, and anakinra
- Also know **PASH** (Pyoderma gangrenosum, Acne, Suppurative Hidradenitis) and **PAPASH** (Pyogenic Arthritis, Pyoderma gangrenosum, Acne, Suppurative Hidradenitis)

## HAIR-AN

- Hyper Androgenism, Insulin Resistance, Acanthosis Nigricans
- Can be considered a unique subtype of PCOS in women
- Treatment: anti-androgens (e.g., spironolactone), OCPs, and insulin-sensitizing meds

## Apert syndrome (acrocephalosyndactyly)

- AD mutation in **fibroblast growth factor receptor 2** (FGFR2);  $\uparrow$ FGFR2 signaling → follicular hyperkeratosis and sebaceous gland hypertrophy
- Synostoses of bones of hands/feet, vertebral bodies, and cranium
- Diffuse distribution of **moderate to severe acne**, especially on extensor arms, buttocks, and thighs
- Nail dystrophy and cutaneous/ocular hypopigmentation
- Treatment: isotretinoin

## Rosacea

#### Epidemiology

- Peaks at 30–40 yo; F > M; usually skin types I and II

### Pathogenesis

- Chronic vascular inflammatory disorder
- Multifactorial: **vascular hyperreactivity**, chronic solar damage, sensitivity to heat, hyperirritable skin, and possible association with *Demodex*

### Clinical features

- Usually limited to central face
- Depends on subtypes (see [Rosacea subtypes](#) section)

### Histopathology

- Perivascular and perifollicular lymphohistiocytic infiltrate, vascular ectasia, mild edema, and sebaceous hyperplasia

### Treatment/clinical course

- **Avoid triggers** (sunlight, heat/cold, stress, strong emotions, alcohol, hot beverages, spicy foods, and chemical irritation) and sunscreen
- Topicals: **metronidazole**, sodium sulfacetamide/sulfur, azelaic acid, benzoyl peroxide, clindamycin, and green-tinted makeup
- Systemic: TCNs, amoxicillin, and isotretinoin if severe
- Others: IPL and PDL (rhinophyma: CO<sub>2</sub> laser and electrosurgery)

### Additional boards factoid

- Haber's syndrome: genodermatosis w/ rosacea-like eruption and verrucous lesions

## Rosacea subtypes

### Erythematotelangiectatic (vascular)

- Central face with recurrent blush that eventually becomes permanent flushing
- Burning, stinging sensation; easily irritated with roughness and scaling
- Can have associated edema
- +/- telangiectasias

### Papulopustular (inflammatory)

- Similar to acne vulgaris, but lesions may have deeper red color and **no comedones**
- Persistent central facial erythema with transient papules/pustules

### Phymatous

- Thickening of skin due to **overgrowth of sebaceous glands**
- Most common on nose (**rhinophyma**); can also involve chin (gnathophyma), forehead (metophyma), earlobes (otophyma), and eyelids (blepharophyma)

### Ocular

- About **50% of rosacea patients** affected
- Many complaints including **dryness, foreign body sensation**, photosensitivity, burning/stinging, blepharitis,

recurrent chalazion, conjunctivitis, keratitis, iritis, and scleritis

- Treatment: **doxycycline/minocycline**

## Rosacea variants

### Solid facial edema in rosacea (Morbihan disease and rosacea lymphedema)

- Unknown etiology; possibly a result of chronic inflammation → obstruction of lymph vessels or fibrosis
  - There is a similar condition in acne
- **Hard non-pitting swelling** of forehead, glabella, nose, and cheeks
- May be more pronounced during **early morning hours**
- ↓vision if eyelids involved
- Spontaneous resolution DOES NOT occur
- ToC = **isotretinoin ± ketotifen** (antihistamine)
  - Other options: systemic steroids, antibiotics, and lymphatic drainage/compression therapy

### Pyoderma faciale (rosacea fulminans)

- **Females** in their 20–30s
- Rapid onset of intensely inflamed coalescent fluctuant nodules and cysts on background of dark red to cyanotic erythema; can have draining sinuses with purulent drainage
- Centrofocal region, no involvement elsewhere and no comedones (vs acne fulminans)
- Most develop **scarring**
- Can have low-grade fever, myalgias, ↑WBC, and ↑ESR
- Treatment (same as acne fulminans): **prednisone** (with slow taper), and **isotretinoin**

### Granulomatous rosacea

- Middle-aged women
- Discrete **yellow/ brown-red firm papules** or nodules on background of diffusely reddened thickened skin on butterfly region; also can be distributed around periphery of face and perioral areas
- On histology, non-caseating epithelioid granulomas; resembles sarcoidosis
- Treatments: TCNs and isotretinoin

### Lupus miliaris disseminatus faciei

- Young adults; more common in **Asians** (especially Japanese)
- Smooth, firm, **yellow-brown to red** 1–3 mm monomorphous papules ([Fig. 3-77](#))
- Present in typical butterfly area of rosacea, but also seen laterally (below mandible) and periorificially
- Especially characteristic is **eyelid skin involvement**
- Heals with **scarring**
- Treatment is difficult; can try isotretinoin and TCNs



**Figure 3-77.** Lupus miliaris disseminatus faciei. (From Andrews et al. Andrews' Diseases of the Skin, 11th Ed. Elsevier. 2011)

### Perioral/periorificial dermatitis

#### Epidemiology

- Young women in their 20–30s
- Children can also be affected

#### Pathogenesis

- Inflammatory condition of unknown cause, perhaps related to rosacea
- Most commonly attributed to use of **topical fluorinated corticosteroids** or facial cosmetics

#### Clinical features

- Clusters of small, pink discrete scaly papules/pustules in perioral region with **clear zone around the vermilion border**
  - Can also involve nasolabial folds and cheeks
- **Burning sensation**, minimal itching

#### Treatment/clinical course

- Self-limited, although resolution can take months to years
- Avoid cosmetics, topical steroids, and other irritating topicals
- TCNs (or erythromycin in pediatrics) for 6–8 weeks with gradual tapering to avoid rapid rebounding
- TCIs, topical antibacterials, and topical metronidazole

#### Variants

- Periorbital/periocular dermatitis
- **Periorificial dermatitis** is a combination of perioral and periorbital/periocular dermatitis

### Folliculitis

#### Superficial folliculitis

- Culture of pustule usually = normal flora
  - When culture is positive, *Staphylococcus aureus* is **most common** infectious etiology
- Perifollicular pustules often with erythematous base in areas with terminal hairs (scalp, beard, trunk, buttocks, and thighs)

- Treatment depends on culture results; if culture-negative: topical benzoyl peroxide, topical antibiotics, and TCNs

#### Gram negative folliculitis

- Occurs in **acne patients receiving prolonged antibiotic treatment** (esp. TCNs)
- Anterior nares become colonized with gram negative organisms (*Proteus*, *Enterobacter*, *Escherichia coli*, or *Klebsiella*)
- More common in adult men
- Numerous pustules on an erythematous base; short-lived, but new lesions continue to appear
- Central region of face, **lesions fan out from nose/mouth** to involve perinasal/beard region
- Pruritic
- ToC = isotretinoin

#### Hot tub folliculitis

- A gram negative folliculitis due to *Pseudomonas aeruginosa*
- Use of hot tub 12–48 h prior to onset
- Edematous pink to red perifollicular papules and pustules on the **trunk**
- **Self-resolves**

#### Eosinophilic folliculitis

- Three forms:
  - Eosinophilic pustular folliculitis (Ofuji's disease)
    - 30 yo; M > F; more common in **Japanese**
    - Recurrent explosive crops of intensely pruritic grouped follicular papules and pustules
      - ◆ Can also have erythematous patches and plaques with superimposed coalescent pustules
      - ◆ Central clearing and centrifugal extension leads to figurate/serpiginous lesions
      - ◆ Most common on face, back, and extensor arms
      - ◆ Peripheral eosinophilia
    - Spontaneous resolution followed by relapses every 3–4 wks
    - Symptomatic treatment of pruritus and **oral indomethacin** may help
  - AIDS-associated eosinophilic folliculitis
    - See Infectious Dermatology chapter
  - Neonatal eosinophilic pustular folliculitis
    - Early in infancy
    - Pruritic perifollicular pustules and vesicles on erythematous base usually on **scalp**
      - ◆ Secondary crusting is common
    - Self-limited, cyclical course for few months to years

#### Disseminate and recurrent infundibulofolliculitis

- Adults with **darkly pigmented skin**
- Hundreds of monotonous 1–2 mm pruritic flesh-colored follicular papules (similar to goose bumps in appearance) on **trunk** > neck and upper extremities



- Lasts months to years
- Treatments: topical corticosteroids, lactic acid creams, and urea creams

### Pseudofolliculitis barbae

- Most common in **African American** curly-haired men who shave their **beard**
- Tightly curled hairs curve back into skin after being shaved → inflammatory reaction with papules/pustules
- Hyperpigmentation, hypertrophic scars, and keloids are possible
- Treatment: **stop shaving**; laser hair removal, chemical depilatories, oral antibiotics and topical corticosteroids for antiinflammatory effects, tretinoin can be used to “toughen” the skin
  - If pt must shave, instruct to gently dislodge ingrown hairs and shave in direction of hair growth

### Acne keloidalis

- Males; **African American** > **Latinos** > **Asians** > **Caucasians**
- Dome-shaped, pruritic, follicular papules on **posterior neck and occipital scalp**
- Develop into **keloidal papules** which coalesce into large plaques in band-like distribution near posterior hairline; cicatricial alopecia in areas of involvement
- Treatment: ↓mechanical irritation to affected areas, tretinoin gel plus potent topical corticosteroid, intralesional corticosteroids, oral or topical antibiotics if inflamed, surgical excision, and CO<sub>2</sub> laser

### Follicular occlusion tetrad (acne conglobata, hidradenitis suppurativa, dissecting cellulitis of the scalp, and pilonidal cyst)

#### Hidradenitis suppurativa (acne inversa)

##### Epidemiology

- Starts after puberty
- F > M, but with severe debilitating disease M > F
- May be more common in African Americans

##### Pathogenesis

- Follicular occlusion + immune dysregulation (both innate and adaptive immunity)
- Familial mutations seen in gamma-secretase
- Associations: obesity, **smoking**, metabolic syndrome, and depression

##### Clinical features

- Affects **apocrine gland-bearing areas** (axilla, inguinal, anogenital, and inframammary)
- Begin as recurrent, tender/painful inflammatory nodules, and **sterile abscesses**
- Later, develop **sinus tracts**, hypertrophic scars, contractures may develop; superficial sinus tracts present as **double-ended comedones**

- Chronic thick viscous suppurative drainage; frequently malodorous; +/- secondary infection
- Anemia, secondary amyloidosis, lymphedema, fistula formation, and SCC due to chronic scarring

##### Histopathology

- Suppurative folliculitis with abscess formation, follicular plugging, granulation tissue, and inflammation that can involve apocrine glands; late stages can have fibrosis

##### Treatment/clinical course

- ↓weight, ↓friction/moisture, oral antibiotics, topical clindamycin, and intralesional or systemic corticosteroids
- **Surgical excision, marsupialization**, CO<sub>2</sub> laser with secondary intention healing, Nd: YAG
- Variable success: isotretinoin, finasteride, cyclosporine, and TNF-α inhibitors

### Pilonidal cyst

- M > F, 20–40 yo
- a/w curly hair, obesity, poor hygiene, and prolonged sitting
- **Painful draining sinus in sacrococcygeal region**
  - Can be filled with nests of hair
- Treatment: surgical excision; if inflamed, oral antibiotics

### Dissecting cellulitis of the scalp and acne conglobata (discussed in Alopecia and Acne sections)

### Other diseases of eccrine and apocrine sweat glands

#### Hyperhidrosis

##### Pathogenesis

- Sweating is a reflex controlled through the sympathetic nervous system; nerves are anatomically sympathetic but functionally cholinergic
- **Primary localized hyperhidrosis is most common type**
- **Secondary hyperhidrosis** is due to an **underlying condition**. There are many causes that can be classified based on the source of neural impulse:
  - **Cortical (emotional)**
    - ↑neural impulses from the cerebral cortex due to emotion or sensory stimuli
  - **Hypothalamic (thermoregulatory)**
    - Due to ↑body temperature or direct hypothalamic stimuli
  - **Medullary (gustatory)**
    - Physiologic medullary hyperhidrosis: afferent impulses from taste receptors stimulate sweating (spicy foods, alcohol, and citrus fruits)
    - Pathologic medullary hyperhidrosis: auriculotemporal or **Frey’s syndrome**
  - **Spinal (cord transection)**
    - Spinal disorders may result in lack of thermal sweating below the injury, hyperhidrosis at the injured level, or other unusual patterns of sweating

- Axon reflex (local inflammatory)
  - Direct stimulation of a sympathetic axon can cause sweating (electrical, physical, or drug-induced)
  - Mediators from inflammatory skin disease (psoriasis and dermatitis) can elicit localized hyperhidrosis

#### Clinical features

- Shiny wet skin surfaces or excessive sweat stains on clothing
- Primary localized hyperhidrosis: **palmoplantar > axillary > forehead**
- Secondary hyperhidrosis: can be localized or generalized
- **Starch-iodine technique** can aid in determining the most active areas

#### Treatment/clinical course

- Topical antiperspirants (**aluminum chloride**), iontophoresis, botulinum toxin, systemic anticholinergics (**glycopyrrolate and oxybutynin**),  $\alpha$ -adrenergic blockers (clonidine), thoracic sympathectomy, and behavioral modification/psychotherapy

## Hypohidrosis and anhidrosis

#### Epidemiology/pathogenesis

- Central or neuropathic diseases (e.g., brain tumors and spinal cord injuries) or meds (e.g., anticholinergics and  $\alpha$ -adrenergic blockers) that disrupt neural impulses
- Congenital alterations of sweat glands (e.g., ectodermal dysplasias)
- Acquired destruction/atrophy of sweat glands (e.g., burns, scleroderma, morphea, and GVHD)
- Sweat gland obstruction (e.g., miliaria, ichthyoses, psoriasis, and eczematous dermatoses)

#### Clinical features

- Skin may appear unremarkable, but there is a ↓ or absence of sweating and resulting **hyperthermia**
- Attempt to induce sweating (exercising in hot room or using electric blanket) followed by starch-iodide technique to demonstrate ↓ or absent sweating

#### Treatment/clinical course

- Discontinue offending meds
- Avoid hyperpyrexia and maintain a cool environment
- Gentle exfoliation if obstructed sweat ducts

## Miliaria

#### Epidemiology

- Most common in **neonates** who have not fully developed eccrine ducts
- **Adults in hot humid climates**

#### Pathogenesis

- Excessive sweating causes maceration of the stratum corneum → eccrine duct obstruction → sweat retention within the duct

#### Clinical features

- [Table 3-29](#)

## Bromhidrosis

- **Apocrine bromhidrosis**: bacterial degradation of apocrine sweat yields ammonia and short chain fatty acids; exaggeration of typical axillary body odor
- Eccrine bromhidrosis: three types
  - Keratogenic: bacterial degradation of stratum corneum macerated by excess eccrine sweat
  - Metabolic: abnormal secretion of amino acids or breakdown products as seen in heritable metabolic disorders (e.g., phenylketonuria has mousy odor and maple syrup urine disease has sweet odor)
  - Exogenous: odorogenic compounds such as garlic, asparagus, and curry

## Chromhidrosis

#### Pathogenesis

- Apocrine chromhidrosis: adrenergic stimuli causes myoepithelial contractions
- Eccrine chromhidrosis: contamination of colorless eccrine sweat by a chromogen

#### Clinical features

- **Colored sweat**
- Apocrine chromhidrosis:
  - Usually on face and axilla
  - Yellow = **lipofuscin**
- Eccrine chromhidrosis:
  - Blue or blue/green = copper
  - Brown = dihydroxyacetone-containing self-tanning products
  - Red = **clofazimine and rifampin**
  - Brown = **ochronosis**

**Table 3-29.** Three Types of Miliaria

Type	Location of Obstruction	Cutaneous Lesions	Patient Population	Most Common Location
Crystallina	Stratum corneum	<b>Non-pruritic, clear</b> , fragile, 1 mm vesicles	Neonates <2 wks of age Children and adults in hot climates	Face and trunk
Rubra	Mid-epidermis	<b>Pruritic, erythematous</b> , 1–3 mm papules; may have pustules	Neonates 1–3 wks of age Children and adults in hot climates	Neck and upper trunk
Profunda	Dermal–epidermal junction	Non-pruritic, white, 1–3 mm papules	<b>Adults in hot climates</b> ; often with multiple bouts of miliaria rubra	Trunk and proximal extremities



**Figure 3-78.** Fox-Fordyce disease. Monomorphic skin-colored papules in the axillary vault. Lesions may be intensely pruritic or patients may be unaware of the condition. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

### Fox-Fordyce disease (apocrine miliaria)

- Plugging of apocrine sweat glands in adolescent/young adult females
- **Extremely pruritic**, skin colored or yellow dome-shaped follicular papules in apocrine areas (axilla > periareolar and anogenital) → ↓hair density (Fig. 3-78)
- Treatment is difficult – options: tretinoin, topical corticosteroids, TCIs, topical antibiotics, and surgical excision; pregnancy can lead to improvement

## 3.14 DRUG REACTIONS

- Cutaneous drug eruptions (CDEs) are one of the most common adverse drug reactions; occur in up to 1% of patients receiving systemic meds
  - Highest risk medications (% on medication that develop rash): **aminopenicillins** (up to 8%) > **anticonvulsants** (5%) > **TMP/SMX** (4%) > **NSAIDs** (0.5%)
- CDEs are divided into **simple** (no visceral/systemic involvement) and **complex** (systemic involvement)
  - 2% of all CDEs are SCARs (severe cutaneous adverse reactions = SJS/TEN, DRESS/DHS, AGEP, anaphylaxis,

**Table 3-30.** Immunologic Drug Reactions

Type	Mechanism	Examples
Type I	IgE-dependent	<b>Urticaria</b> , angioedema, anaphylaxis
Type II	Cytotoxic (due to antibodies directed against fixed antigens)	Drug induced thrombocytopenia
Type III	Immune-complex dependent	Serum sickness, <b>vasculitis</b> , some urticarias
Type IV	Delayed type/cell-mediated	<b>Morbilliform</b> , FDE, lichenoid drug, SJS/TEN

anticoagulant-induced skin necrosis, and generalized FDE)

○ SCARs are seen in 1/1000 hospitalized patients

- Three most common morphologies: **morbilliform** (>92%) > urticarial (6%) > vasculitis (2%)
- May be immunologically-mediated (Table 3-30) or non-immunologic (overdose, pharmacologic SEs, cumulative toxicity, delayed toxicity, drug-drug interactions, alterations in metabolism, and exacerbation of existing disease)
- **HIV(+)** patients have ↑↑incidence of CDEs
  - Occurs in 1/1000 HIV pts per year (vs 1 per million in general population)
  - Highest risk when CD4 count is 100–400/mm<sup>3</sup>
  - Most common: **TMP/SMX** (rash in 40% of HIV pts), dapsone, β-lactams, **nevirapine**, **abacavir**, and anticonvulsants

### Morbilliform (aka exanthematous or maculopapular drug eruption)

- **Most common drug reaction** affecting skin; mechanism = cell-mediated hypersensitivity; onset typically 7–14 days after drug initiation
- Most common culprit drugs (all lead to CDE in >1% of pts): **β-lactams** (PCNs and CSNs), **TMP/SMX**, **anticonvulsants**, and **allopurinol**
- Viral infections ↑ incidence of drug reactions:
  - **Ampicillin** in pts w/ EBV-mononucleosis → rash in ~100% of children and up to 70% adults
  - Up to 40% of **AIDS** pts get rash to **TMP/SMX**
- Rash starts w/ red-pink macules and papules in **groin/axilla** → later, symmetrically-distributed red macules and papules on trunk and upper extremities, often w/ significant **pruritus** (helps DDx from viral exanthem) +/- low-grade fever → rash becomes confluent over time; lower extremities may have purpuric lesions; **sparing mucous membranes**; eruption subsides 1–2 weeks after drug cessation
  - Features concerning for SCAR: **facial edema** or peripheral **eosinophilia** (DRESS); mucosal involvement or **dusky/painful skin** (early SJS/TEN)
- Histopathology: mild basal vacuolar and spongiotic changes with a few necrotic keratinocytes (50%), superficial to mid dermal perivascular lymphohistiocytic infiltrate with some eosinophils
- Rx: supportive, with topical steroids and anti-pruritics; stop drug usually, but may attempt to “treat through” if drug is essential (very low rate of progression to SJS/TEN)

## Urticaria, angioedema and anaphylaxis

- See [Urticaria and Angioedema](#) section

## Drug-induced hypersensitivity syndrome/ drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS)

- Severe systemic drug reaction with **10% mortality**
- Incidence up to 1/1000 pts on anticonvulsants or sulfonamides, with ↑risk in African Americans
- Develops **2 to 6 weeks** after initiation of drug (later than other drug reactions)
- Most common symptoms = **fever** (85%) and **morbilloform skin eruption** (75%); also see lymphadenopathy, arthralgias (> arthritis), **multi-organ involvement** ([Table 3-31](#)) (**liver** most common and most severe, followed by **kidney**), peripheral **eosinophilia** (>1500 absolute eosinophils), mononucleosis-like **atypical lymphocytosis**
- Rash starts on **face and upper trunk/extremities**; appears morbilliform at onset → becomes **edematous** (facial edema is classic early clue!), with follicular accentuation +/- tense vesicles/bullae, pustules, and purpuric lesions
- Late sequelae: **thyroiditis/Graves' syndrome**, SIADH, and diabetes
- Risk factors:
  - **HLA-A\*3101** (Northern Europeans on carbamazepine)
  - **HLA-B-5801** (Han Chinese on allopurinol)
  - Inability to detoxify **arene oxide** metabolites (phenobarbital, phenytoin, and carbamazepine)
  - **Slow acetylators** (sulfonamides)
  - Possible role for **HHV-6 reactivation** (> HHV-7, CMV, and EBV)
- Most common meds: **aromatic anticonvulsants** (phenytoin, carbamazepine, and phenobarbital; **all cross-react**), lamotrigine (when coadministered with valproate), **sulfonamides**, **minocycline**, **dapsone**, **allopurinol**, **abacavir**, and **nevirapine**
- DIHS variants:
  - **Anticonvulsant hypersensitivity syndrome**: ↑risk if cannot detoxify **arene oxide** metabolites; liver involvement in 70%; less common to have kidney, lung or heart involvement; switch to **valproic acid** or **levetiracetam** instead of aromatic anticonvulsants

**Table 3-31.** Visceral Involvement in Drug Induced Hypersensitivity Syndromes

Medication	Clinical Abnormality
Allopurinol	Renal
Ampicillin	Cardiac
Carbamazepine	Renal
Dapsone	Hepatic and renal
Minocycline	Hepatic, pulmonary, and cardiac
Phenytoin	Hepatic

(From *DRESS syndrome : Part I. Clinical perspectives*. Husain Z., Reddy B.Y., Schwartz R.A. *Journal of the American Academy of Dermatology*. Elsevier. Volume 68, Issue 5. pp 693.e1-693.e14. 2013.)

- **Allopurinol hypersensitivity syndrome**: usually seen in **renal failure** pts; ↑↑risk for Han Chinese with **HLA-B-5801**; liver involvement in 70%; **kidney** in up to 80%; also a/w **pancreatitis** and **diabetes**; rare to have lung or lymph node involvement; 25% mortality
- **Sulfonamide hypersensitivity syndrome**: ↑risk if **slow acetylators**
- **Dapsone hypersensitivity syndrome**: concomitant **hemolysis and methemoglobinemia** common (due to dapsone effect) → ↑bilirubin → **icterus**; lymphadenopathy in 80%; **lacks eosinophilia**; liver involvement can be fatal
- **Minocycline hypersensitivity syndrome**: typically seen in **young adults** undergoing acne treatment; F > M; a/w **glutathione S-transferase deficiency**; strong a/w **interstitial eosinophilic pneumonia**; **liver involvement** in 75%; renal involvement in up to 20%
- Treatment: **stop med** + superpotent topical steroids (skin-limited disease) + **systemic steroids if lung and heart involvement** (not helpful for renal and liver involvement)
  - **Relapse common** if steroids tapered too rapidly → usually give for weeks to months
  - Use **valproic acid** or **levetiracetam** in place of aromatic anticonvulsants

## AGEP

- Acute, febrile pustular drug eruption that mimics von Zumbusch pustular psoriasis
- **>90% are drug-induced**
  - Other causes: **mercury** exposure, radiocontrast, or enterovirus
  - Occurs rapidly (<4 days) after drug administration
- p/w **high fever** and small (<5 mm) non-follicular, **sterile pustules** arising on background of edematous red skin; most commonly begins on **face and intertriginous sites** → generalizes within hours
  - 50% of pts have purpuric or EM-like lesions, mucosal involvement, **edema of hands/face**, or bullae → these findings help DDx from pustular psoriasis
  - ↑↑↑WBC count with peripheral **neutrophilia** +/- eosinophilia, **hypocalcemia**, and renal insufficiency
- **Patch test positive** in majority (50%–60%)
- Most common drugs: **β-lactam** (PCNs and cephalosporins) and **macrolide antibiotics** > CCBs (diltiazem most common) and antimalarials
- Histopathology: subcorneal and **intraepidermal spongiform pustules**, **prominent superficial dermal edema**, and perivascular mixed inflammatory infiltrate with eosinophils
  - Presence of **edema and eosinophils**, and lack of significant acanthosis helps differentiate from pustular psoriasis
- Rx: stop drug, supportive therapy with topical steroids and antipruritics

## Photosensitive drug reactions

- Due to exogenous photosensitizing agents (meds); may be either phototoxic (most common) or photoallergic



- **Phototoxic:** common and predictable; occurs in **anyone** who receives enough drug and UVR; most commonly due to **systemic** meds
  - Mechanism: direct interaction between UVR (**UVA most common**) and drug/drug metabolites → free radicals → damage to skin cells
  - p/w painful **exaggerated sunburn-like** eruption +/- blistering within **hours** → heals with **hyperpigmentation**
  - Histopathology (same as sunburn): necrotic keratinocytes ("**sunburn cells**"), dermal edema, minimal dermal inflammation, and vasodilation
  - Most common drugs: **tetracyclines** (demeclocycline > doxycycline > TCN >>> minocycline), NSAIDs (naproxen and piroxicam), **fluoroquinolones**, amiodarone, **psoralens**, phenazothiazines (chlorpromazine and prochlorperazine), **voriconazole** (XP-like presentation w/ ↑↑risk of aggressive SCC, eruptive lentiginos, premature aging, and early death), St. John's wort, and **HCTZ**
  - Clinical variants:
    - Pseudoporphyria
      - ◆ Causes: NSAIDs (**naproxen is #1**), thiazides, **voriconazole**, furosemide, TCNs, nalidixic acid, and tanning bed exposure; may also occur in hemodialysis pts
      - ◆ Skin findings similar to PCT, but **lacks hypertrichosis, sclerodermoid features, and hyperpigmentation**
      - ◆ Normal porphyrin studies
      - ◆ Histology: similar to PCT
    - Photoonycholysis (**psoralens** and TCNs)
    - Slate gray hyperpigmentation (**amiodarone**, TCAs, and diltiazem)
    - Photolichenoid eruptions (**HCTZ** and NSAIDs most commonly)
    - UV recall (**MTX**)
    - Phytophotodermatitis (**furocoumarin**-containing plants = parsley, celery, lime, fig, and yarrow)
- **Photoallergic:** less common, but more chronic than phototoxic; idiosyncratic; only occurs in **sensitized** patients (delayed-type hypersensitivity); often persists after withdrawal of med; most commonly due to **topical** photoallergens
  - Mechanism: cell-mediated hypersensitivity; UVR (**especially UVA**) induces chemical change in drug → becomes photoallergen; **requires sensitization** with **7–10 day incubation period**
  - p/w itchy, eczematous to lichenoid eruption on sun-exposed areas initially → later spreads to non-sun-exposed sites; less likely to be bullous than phototoxic rxns
  - Histopathology: spongiotic dermatitis, superficial perivascular inflammation with eosinophils
  - Most common drugs: sunscreens containing **oxybenzone** (benzophenone-3) > fragrances (6-methyl coumarin, **musk ambrette**, and sandalwood oil), NSAIDs (**piroxicam** (patch positive to thimerosal) and **ketoprofen**), griseofulvin, quinidine/quinine, sulfonamides, and quinolones

- Diagnosis confirmed by **photopatch testing** (utilizing UVA)

## Drug-induced pigmentary changes

- **Hyperpigmentation:**
  - May be localized or generalized; often **photodistributed**
  - Arises by many mechanisms, including: 1) drug/drug metabolite deposition, 2) induction of melanin production, 3) post-inflammatory changes due to photosensitive eruptions
  - Often a/w **melanonychia** (longitudinal, diffuse, or transverse) and/or **oral pigmentation**
  - Most common drugs: **minocycline**, chemotherapeutics, and **AZT** (zidovudine), **antimalarials**, and heavy metals
  - Usually reversible, but may take months to years
- **Hypopigmentation:**
  - Most frequently due to **topical meds**, but also seen with **tyrosine kinase inhibitors** (**imatinib** most commonly; due to inhibition of KIT receptor inhibition, which is involved in melanogenesis)
  - May be a/w lightening of hair
  - Most common agents: 1) **phenols/catechols** (includes hydroquinone, MBEH, MMEH, various phenol derivatives, and p-cresol); 2) **sulphydryls** (includes methimazole) and; 3) **miscellaneous drugs** (PPD, corticosteroids, azelaic acid, benzyl alcohol, **tyrosine kinase inhibitors**, mercurials, arsenic, thiotepa, and phosostigmine)
  - **Reversible, except MBEH** (permanent depigmentation at application site and distant skin)

## Bullous drug reactions (discussed in Blistering Diseases section)

## Lichenoid drug eruptions (discussed in Lichenoid Dermatitis section)

## Other drug eruptions (Table 3-32)

## 3.15 PHOTODERMATOSES AND OTHER PHYSICAL DERMATOSES

### Temperature-related dermatoses

#### Thermal burns

- Arise due to excess heat on skin
- **First degree:** erythema + epidermal peeling (e.g., ordinary sunburn)
- **Second degree:** two forms
  - Superficial: **painful** vesicles due to edema of superficial dermis and epidermis; **non-scarring**; may take 3 weeks to heal
  - Deep: pale, **anesthetic** skin; **results in scarring** (due to reticular dermis/appendageal injury)

*text continued on p. 165*

**Table 3-32.** Drug Eruptions Not Covered Elsewhere

Disease	Clinicopathologic Features	Most Common Drugs
Coumadin-induced skin necrosis	Rare, life-threatening reaction; <b>begins 2–5 days after drug initiation, when protein C levels at nadir</b> ; ↑risk in pts with pre-existing protein C deficiency (hereditary or acquired); initially p/w painful red plaques → <b>hemorrhagic bullae, ulcers on fatty areas</b> (breast, buttocks, thighs); Rx: stop warfarin, give vitamin K, heparin and IV infusions of protein C; <b>histology: non-inflammatory thrombotic vasculopathy</b> (multiple fibrin thrombi in dermal/SQ vessels), lacks LCV	Coumadin (occurs in 1/10,000 pts)
Heparin-induced skin necrosis (heparin-induced thrombocytopenia with thrombosis syndrome)	Systemic syndrome that p/w ↓ <b>PLT levels, thrombosis and cutaneous necrosis</b> ; mechanism = <b>autoantibodies against heparin/platelet factor 4 complexes</b> → bound antibodies lead to PLT aggregation and consumption → thrombocytopenia and clotting (due to PLT aggregates); histology: thrombotic vasculopathy with PLT aggregates (usually not easily seen on H&E); Rx: stop heparin, start direct thrombin inhibitor or factor Xa inhibitor	Unfractionated heparin (>fractionated LMWH)
Bromoderma and Iododerma	<b>Acneiform lesions</b> , papulopustules, nodules, <b>vegetating lesions</b> simulating P. Vegetans or blastomycosis; clear or hemorrhagic blisters (iododerma > others); skin lesions usually appear after chronic exposure; histology: <b>PEH with intraepidermal neutrophilic microabscesses</b> and dense dermal neutrophilic inflammation (need bug stains to r/o deep fungal)	Bromide, iodine-containing radiocontrast, iodine-containing drugs (amiodarone, SSKI, iodine nutritional supplements, povidone-iodine)
<b>Drug-Induced Hyperpigmentation</b>		
Chemotherapy	<b>BCNU (carmustine) and nitrogen mustard (mechlorethamine)</b> : hyperpigmentation at <b>sites of topical application</b> ; ↑melanocytes and melanin in keratinocytes <b>Bleomycin (IV or IL)</b> : linear or <b>flagellate</b> hyperpigmented patches on <b>trunk</b> ; hyperpigmentation of palmar creases and skin overlying joints; may be a/w minor trauma/ <b>scratching</b> ; transverse melanonychia; <b>sclerodermoid</b> changes; ↑melanin in keratinocytes but normal # melanocytes <b>Busulfan</b> : Addison's-like generalized hyperpigmentation +/- <b>pulmonary fibrosis</b> ; ↑melanin in keratinocytes + dermal melanophages <b>Cyclophosphamide</b> : diffuse mucocutaneous hyperpigmentation or localized hyperpigmentation in nails, teeth, palms/soles; resolves within 12 mos <b>Ifosfamide</b> : related to cyclophosphamide – hyperpigmentation of flexural areas, hands, feet, scrotum, and under occlusive dressings (like thiotepa) <b>5-FU</b> : <b>phototoxic</b> dermatitis followed by hyperpigmentation (following systemic 5-FU) or <b>serpentine hyperpigmentation overlying veins</b> that were infused; histology: necrotic k'cytes, pigment incontinence, ↑melanin in basal k'cytes <b>Hydroxyurea</b> : early <b>lichenoid/DM-like</b> eruption overlying joints → PIH at involved sites; melanonychia, lunula hyperpigmentation <b>Imatinib</b> : generalized or localized <b>depigmentation</b> (40%; due to blockade of c-KIT) <b>Sunitinib</b> : depigmentation of hair and yellowing of skin <b>MTX</b> : <b>phototoxic dermatitis</b> → PIH <b>Dactinomycin</b> : reversible hyperpigmentation of face (> generalized) <b>Doxorubicin</b> : hyperpigmentation on skin of <b>dorsal hands/joints</b> , palmar creases, oral mucosa and soles; transverse melanonychia; ↑melanocytes and melanin in k'cytes	
Antimalarials	<b>Hyperpigmentation occurs in 25% of pts</b> taking antimalarials; does <b>not</b> fully resolve after drug d/c; Histology: deposition of <b>drug-melanin complexes (Fontana Masson+)</b> and <b>hemosiderin (Perls+)</b> in dermis <b>Chloroquine/hydroxychloroquine</b> : blue-black to gray hyperpigmentation on <b>pretibial area</b> (most common presentation, looks identical to <b>type II minocycline</b> hyperpigmentation of shins) > face, oral mucosa (subungual and hard palate), sclera <b>Quinacrine</b> : diffuse <b>yellow-brown</b> discoloration of skin and eyes (mimics jaundice)	Chloroquine, hydroxychloroquine, quinacrine
Heavy metals	<b>Arsenic</b> : hyperpigmentation patches with superimposed <b>“raindrops” of hypopigmentation</b> ; most commonly <b>intertriginous</b> sites, <b>palms/soles</b> , pressure points; occurs up to <b>20 yrs after</b> exposure (strongly dose-dependent); <b>PPK</b> and <b>SCC</b> arise after hyperpigmentation stage; histology: deposits of arsenic in dermis and epidermis + ↑melanin in keratinocytes <b>Bismuth</b> : generalized blue-gray discoloration on head/neck, dorsal hands, oral mucosal; histology: dermal bismuth deposits <b>Gold (chrysiasis)</b> : <b>permanent blue-gray hyperpigmentation</b> on <b>face (pericoular #1)</b> and other sun-exposed sites; histology: gold deposits in macrophages in perivascular/peri-eccrine distribution; particles have orange-red birefringence on polarized light; <b>does not bind to BMZ or eccrine membrana propria</b> (distinguishes from argyria) <b>Iron</b> : arises after injection of iron, use of <b>Monseil's</b> solution (ferric subsulfate), post-sclerotherapy, or in setting of chronic stasis or PPD; histology: dermal hemosiderin ( <b>+Perls</b> ) deposits on collagen fibers and in macrophages <b>Lead</b> : <b>lead lines</b> (on gingival margins); histology: subepithelial lead deposits <b>Mercury</b> : Topical mercury ointments (no longer used) lead to slate-gray discoloration; histology: <b>huge deposits</b> (300 μm) of brown-black mercury granules within macrophages in superficial dermis Mercury ingestion (due to teething powders for babies) → <b>acrodynea</b> (acral sites are dusky red and painful) Accidental implantation (broken thermometers) → sclerosing granulomatous nodules <b>Silver (argyria)</b> : <b>diffuse slate-gray pigmentation</b> , with accentuation in <b>photo-exposed</b> areas; due to silver in alternative meds/ <b>elixirs</b> and <b>silver sulfadiazine</b> on burn wounds; +/-scleral and nail hyperpigmentation; histology: deposits of silver bound to <b>BMZ and membrana propria of eccrine glands</b> (best seen with darkfield microscopy)	

Continued

**Table 3-32.** Drug Eruptions Not Covered Elsewhere—cont'd

Disease	Clinicopathologic Features	Most Common Drugs
OCPs	p/w <b>melasma</b> +/- <b>nipple hyperpigmentation</b> and darkening of nevi; histology: ↑melanocyte #, ↑melanin production	
Amiodarone	Up to <b>60%</b> of all pts treated for >3–6 mos will develop hyperpigmentation; most commonly p/w <b>phototoxic eruption</b> (erythema) of <b>face</b> (>other photo-exposed areas) → a smaller subset of cases develop <b>slate-gray</b> discoloration; most common after <b>long-term</b> use of amiodarone; hyperpigmentation <b>fades slowly</b> after drug d/c; histology: unique appearing <b>yellow-brown</b> granules of <b>lipofuscin (Fontana Masson+)</b> in macrophages in perivascular distribution; EM shows <b>lipid-like lysosomal inclusions</b> (unique!)	
AZT (zidovudine)	<b>Widespread mucocutaneous hyperpigmentation</b> (reversible) with accentuation in <b>photo-exposed</b> sites and sites of friction; frequent <b>longitudinal melanonychia</b> (> transverse or diffuse); histology: dermal melanophages, ↑melanin in keratinocytes	
Clofazimine	Most commonly seen in setting of <b>leprosy</b> treatment; similar to minocycline, may have <b>diffuse (red-brown</b> color of skin and <b>conjunctivae)</b> or <b>lesional</b> hyperpigmentation ( <b>blue-gray</b> discoloration of <b>face</b> ); histology: birefringent red crystals of clofazimine seen in perivascular distribution on fresh frozen tissue only (routine H&E fails to demonstrate)	
Diltiazem	Occurs in <b>dark-skinned</b> pts (Fitz IV–VI); ↑risk in <b>African Americans</b> ; slate-gray discoloration on <b>photo-exposed</b> skin with reticular or perifollicular pattern; histology: lichenoid dermatitis with melanophages	
Hydroquinone	Two mechanisms: irritant contact dermatitis (→PIH), or <b>exogenous ochronosis</b> ; histology: exogenous ochronosis demonstrates <b>yellow-brown, banana-like</b> deposits in dermis; hyperpigmentation fades after drug d/c	
Imatinib	Gingival and tooth hyperpigmentation; melanonychia (diffuse); <b>HYPOpigmentation</b> of skin Of note, also a/w <b>periorbital edema</b>	
Minocycline	Typically after <b>long-term</b> use, since dose related (except type I); 40% get hyperpigmentation within 1 yr; <b>oral mucosae, sclerae, nails, bones, cartilaginous sites (ear), and teeth</b> may also be affected; typically fades slowly after drug d/c; may treat with Q-switched lasers <u>Type 1</u> : focal blue-black hyperpigmentation at <b>sites of inflammation or scars</b> (esp. acne); not dose-related; Histology: dermal deposits of drug complexes with <b>iron/hemosiderin (Perls+)</b> <u>Type 2</u> : circumscribed blue-gray <b>“bruise-like”</b> hyperpigmentation of <b>pretibial area</b> and arms; Histology: dermal deposits are drug complexes with both iron/hemosiderin ( <b>Perls+</b> ) and melanin ( <b>Fontana Masson+</b> ) <u>Type 3</u> : diffuse <b>brown</b> hyperpigmentation of <b>sun-exposed</b> areas; due to low-grade phototoxic dermatitis; ↑melanin in basal k'cytes, dermal melanophages/melanin ( <b>Fontana Masson+</b> )	<b>Boards Factoid</b> : fetal exposure to TCN class stains the teeth at different locations: <b>Minocycline</b> = <b>Midportion</b> TCN = gingival one third
Prostaglandin analogs	<b>Periocular hyperpigmentation</b> , eyelash hypertrichosis, and <b>iris hyperpigmentation</b> may follow use of glaucoma meds; self-resolve upon drug d/c	Prostaglandin F-2α analogs ( <b>bimatoprost, latanoprost</b> )
Psoralens	May be <b>diffuse</b> (systemic PUVA) or <b>focal</b> hyperpigmentation (topical PUVA or phytophotodermatitis due to psoralen-containing plants); histology: ↑melanin in k'cytes, dermal melanophages	
Anti-psychotics and anti-depressants	Progressive <b>blue-gray</b> hyperpigmentation in <b>photo-exposed</b> skin; histology: refractile golden brown granules ( <b>Fontana Masson+</b> , Perls negative) in macrophages in perivascular distribution	<b>Phenothiazines</b> (thioridazine, chlorpromazine, promethazine), <b>TCAs</b>
<b>Chemotherapy-Related Drug Reactions</b>		
Toxic erythema of chemotherapy (TEC)	Umbrella term that encompasses a variety of clinical variants of chemotherapy-induced CDEs; chemotherapeutics concentrate into eccrine glands → <b>direct toxic effect</b> on <b>eccrine glands</b> (> epidermis) leads to rash; all variants of TEC have <b>overlapping clinical features (acral dysesthesia, red swollen hands, morbilliform eruption on trunk, prominent desquamation)</b> and similar histologic features (epidermal dysmaturation, scattered necrotic k'cytes and eccrine glandular cells, squamous metaplasia of eccrine glands); starts <b>days-months</b> after drug initiation; Rx: supportive care <u>TEC variants</u> : eccrine squamous syringometaplasia, <b>neutrophilic eccrine hidradenitis</b> , palmoplantar erythrodysesthesia/hand-foot syndrome/acral erythema, <b>Ara-C ears</b> , pseudocellulitis	<b>Most common: Cytarabine/ Ara-C (#1), taxanes</b> (atypical hand/foot syndrome with red plaques on dorsal hands/Achilles tendon/malleoli, nail toxicity +/- paronychia), <b>anthracyclines</b> (doxo/dauno/idarubicin), <b>5-FU</b> <u>Others</u> : capecitabine (5-FU prodrug), MTX, busulfan, cisplatin, cyclophosphamide, gemcitabine, topotecan
Hand-foot skin reaction (HFSR)	Clinically similar to acral erythema variant of TEC but less severe acral dysesthesia and hand swelling; classic feature is <b>prominent hyperkeratotic plaques</b> on areas of friction; Rx: tazarac, 40% urea and efudex (treats hyperkeratosis)	<b>Multi-kinase inhibitors</b> (sorafenib, sunitinib, VEGF inhibitors)
Radiation enhancement and recall	<u>Radiation enhancement</u> : doxorubicin, hydroxyurea, taxanes, 5-FU, etoposide, gemcitabine, MTX <u>Radiation recall</u> : <b>MTX</b> , other chemotherapeutics, high dose IFN-α, simvastatin <u>Sunburn recall</u> : <b>MTX</b>	<b>MTX</b> (radiation recall) is most important for boards
Photosensitivity	Phototoxic eruption on sun-exposed areas	<b>5-FU</b> (and 5-FU prodrugs), <b>MTX, hydroxyurea</b> , docetaxel, dacarbazine
Alopecia	<b>Anagen effluvium</b> is one of most common side effects of most chemotherapies; <b>scalp</b> most commonly (> eyebrows, axillary, pubic hairs); <b>reversible</b> ; hairs may re-grow curly	Reversible alopecia: most chemotherapeutics Irreversible alopecia: <b>busulfan</b> , docetaxel

**Table 3-32.** Drug Eruptions Not Covered Elsewhere—cont'd

Disease	Clinicopathologic Features	Most Common Drugs
Mucositis	Oral and GI tract most frequently affected mucosal sites ( <b>stomatitis</b> most common, 40%); may be severe and dose-limiting; mainly due to direct toxic effect on rapidly-dividing mucosal epithelial cells; <b>starts within first week</b> ; resolves within 3 wks; Rx: oral hygiene, antimicrobials to ↓ secondary infections (Candida, HSV), <b>palifermin</b> (keratinocyte growth factor)	Most chemotherapeutic agents
Extravasation reactions	Ulcerations and/or indurated red plaques at sites of chemotherapy <b>leakage</b> from infusion	<b>5-FU, anthracyclines</b> (doxo + daunorubicin), carmustine, vinblastine, vincristine (of note, can also cause peripheral neuropathy), mitomycin C
Chemotherapy recall	Tender sterile inflammatory nodules at sites of previous chemotherapy drug leakage or prior infusion sites	5-FU, mitomycin C, paclitaxel, anthracyclines
Nail hyperpigmentation (melanonychia)	Longitudinal, transverse or generalized melanonychia	<b>Doxorubicin (#1), 5-FU</b> , cyclophosphamide, hydroxyurea, bleomycin
Inflammation of AKs	AKs become inflamed	<b>5-FU</b> (and 5-FU prodrugs)
Inflammation of DSAP	DSAP lesions become inflamed	<b>5-FU</b> (and 5-FU prodrugs), taxanes
Inflammation of SKs	Seborrheic keratoses become inflamed	Cytarabine, taxanes
Important reactions to specific agents ( <b>Boards Favorite!</b> )	Serpentine suprapurpuric hyperpigmentation (overlying infused veins): <b>5-FU</b> Onycholysis (painful and hemorrhagic): <b>taxanes</b> Exudative hyponychial dermatitis: combination of <b>docetaxel</b> and <b>capecitabine</b> (setting of breast cancer) Lower extremity/foot ulceration: <b>hydroxyurea</b> Dermatomyositis-like eruption: <b>hydroxyurea</b> Necrosis of psoriatic plaques: high-dose <b>MTX</b> (seen in setting of pre-existing psoriasis) Alternating dark and light bands of hair ("flag sign"): <b>MTX</b> Oral leukoplakia resembling flat warts: <b>palifermin</b> Flushing: <b>asparaginase</b> , high-dose BCNU Urticaria: asparaginase Acquired cutaneous adherence/"sticky skin syndrome": combination of <b>doxorubicin + ketoconazole</b> Sclerodermoid reaction (lower extremities most common): <b>taxanes</b> Palmoplantar hyperkeratosis: <b>capecitabine</b> Flagellate hyperpigmentation: <b>bleomycin</b> >> docetaxel Raynaud's syndrome +/- digital necrosis: <b>bleomycin</b> Aral sclerosis: <b>bleomycin</b> Hyperpigmentation of occluded skin: <b>thiotepa</b> (seen in 80% of pediatric pts; starts as diffuse erythema → resolves with hyperpigmentation)	
Interferon reactions	Vasculopathy, necrosis, psoriasis exacerbation, <b>cutaneous sarcoid</b>	
IL-2 reactions	Granulomatous eruption, lobular panniculitis	
Sorafenib reactions	Multi-tyrosine kinase inhibitor; may result in <b>PPK, acral/facial erythema, SCCs, KAs</b> , fingernail splinter hemorrhages, <b>wart-like squamoproliferative lesions</b> , scalp pruritus, flushing, alopecia (also seen in sunitinib), stomatitis (also seen in sunitinib), KP-like eruption (also seen in sunitinib), nipple hyperkeratosis (also seen in sunitinib)	Sunitinib is a multi-kinase inhibitor like sorafenib – it can cause depigmentation of the hair, facial edema, <b>yellow skin pigmentation</b> , hand-foot skin reactions (similar to sorafenib; with painful patches on high friction areas like the heels)
Melanonychia	See nail section	<b>Chemotherapeutic agents</b> (doxorubicin, 5-FU), zidovudine ( <b>AZT</b> ), <b>psoralens</b>
Discoloration other than melanin	See nail section	<b>Minocycline, antimalarials</b> , gold
Paronychia and periungual pyogenic granulomas	See nail section	<b>Retinoids (isotretinoin)</b> , HAART drugs ( <b>indinavir</b> , efavirenz, lamivudine), <b>EGFR inhibitors</b> , MTX, sirolimus, capecitabine
Ischemic changes	Raynaud's, digital ischemia	<b>β-blockers, bleomycin</b>
<b>Injection site reactions</b>		
Vitamin K	Red annular plaques, or <b>Texier's disease</b> (indurated/morpheaform plaques)	
Heparin/LMWH	Necrosis, ecchymosis, calcinosis cutis	

Continued



**Table 3-32. Drug Eruptions Not Covered Elsewhere—cont'd**

Disease	Clinicopathologic Features	Most Common Drugs
Cosmetic dermal fillers (HA, silicone)	Swelling, <b>granulomas</b> , dermal sclerosis	
Corticosteroids	Dermal and <b>SQ fat atrophy</b> , <b>vascular ectasias</b> , hypopigmentation	Kenalog
Vitamin B12	Pruritus, indurated morpheaform plaques	
Vaccines containing aluminum	<b>Granulomatous nodules</b>	
Glatiramer acetate	Immunomodulator (SQ injection) used as in treatment of multiple sclerosis; p/w dermal fibrosis, panniculitis/SQ atrophy, vasospasm	
Embolia cutis medicamentosa (Nicolau syndrome)	May occur with virtually <b>any intramuscular-injected med</b> ; due to <b>vascular thrombosis</b> from periarterial injection; p/w <b>severe pain, ischemia, and pallor of injection site within minutes</b> → progresses to purple, livedoid plaques with dendritic borders, then <b>ulcerates</b> ; Rx: supportive surgery if severe necrosis (amputation may be required)	Wide variety of meds (NSAIDs, vaccines, antibiotics, corticosteroids, IFN, Depo-Provera, local anesthetics)
<b>Other drug reactions</b>		
Gingival hypertrophy	Typically occurs in first year of drug; starts in <b>interdental papillae</b> of the <b>front teeth</b> , on labial side → may progress to involve rest of teeth with multinodular overgrowth of gums; <b>spares edentulous areas</b> ; degree of hyperplasia strongly correlated with <b>poor oral hygiene</b> ; histology: excess buildup of otherwise normal gum tissue; Rx: strict oral hygiene, drug d/c, surgical removal if all else fails	<b>Phenytoin (most common, 50%) &gt; nifedipine (25%) and cyclosporine (25%)</b> Less common: other anticonvulsants, other CCBs, lithium, amphetamines, OCPs
Mucositis	p/w <b>buccal</b> and <b>tongue</b> erosions and ulcerations; <b>foscarnet may give penile ulcerations</b>	Mostly due to <b>chemotherapy</b> or <b>immunosuppressive</b> drugs (5-FU, MTX, doxorubicin)
Alopecia	Drug-induced alopecia is non-scarring, diffuse, and reversible; two main types: <u>Telogen effluvium</u> : <b>delayed</b> (2–4 mos after starting med) diffuse non-scarring alopecia <u>Anagen effluvium</u> : <b>rapid</b> (within 2 wks of starting med) diffuse non-scarring alopecia; due to rapid cessation of cell division (mitoses) within hair matrix	<u>Telogen effluvium</u> : <b>Heparin, β-blockers, IFN, lithium, retinoids</b> , OCP discontinuation, antidepressants, anticonvulsants, ACE inhibitors, colchicine, NSAIDs <u>Anagen effluvium</u> : <b>Chemotherapy, heavy metals</b> (arsenic, gold, thallium, bismuth)
Pseudolymphoma (cutaneous lymphoid hyperplasia)	Medication leads to immune dysregulation → aberrant proliferation of <b>polyclonal</b> B- and/or T-lymphocytes, hypergammaglobulinemia; p/w <b>solitary</b> or multiple grouped (> widespread) firm red to <b>plum-colored</b> plaques and nodules lacking surface changes; most commonly affects “upper half of body:” <b>face, neck, upper extremities, upper trunk</b> ; +/- <b>lymphadenopathy</b> ; Rx: self-resolving; subsides within weeks of drug d/c Histology: <u>T-cell pseudolymphoma</u> : resembles MF with band-like lymphoid infiltrate at DEJ, epidermotropism and lymphocytic atypia (cerebriform nuclei); usually <b>polyclonal</b> (but occasionally clonal → use clinical judgment to DDx from MF) <u>B-cell pseudolymphoma</u> : dense dermal <b>mixed infiltrate</b> (lymphocytes > eosinophils, plasma cells) with <b>Grenz zone</b> ; dermal infiltrate is organized as multiple <b>large blue nodules (follicles)</b> throughout the dermis and superficial fat +/- pale-appearing <b>germinal centers</b> (with <b>tingible body macrophages</b> ) within the follicles; a <b>mantle zone</b> of normal-appearing lymphocytes surrounds the follicles (unlike true B-cell lymphoma); <b>mixture of κ and λ</b> seen on IHC; <b>never see clonality by IGH</b> gene rearrangement	<b>Anticonvulsants</b> (phenytoin, phenobarbital, carbamazepine, lamotrigine), <b>neuroleptics</b> (promethazine, chlorpromazine), <b>ARBs</b> , imatinib, antibiotics (TMP/SMX, CSNs), antidepressants, antihistamines, β-blockers, CCBs, statins, NSAIDs, benzodiazepines <u>Other common causes</u> : <b>Arthropod bite/infestation, Borrelia, tattoo reaction, HSV, HIV, post-zoster</b> (dermatomal), vaccinations (hepatitis A and B)
Serum sickness eruption	Morbiliform-urticarial plaques or <b>vasculitis</b> ; p/w fever, <b>arthralgias</b> , arthritis, lymphadenopathy, <b>renal disease</b> , <b>hypocomplementemia</b> , <b>circulating immune complexes</b> ; due to administration of <b>non-human proteins</b> ; histology: LCV	<b>Anti-thymocyte globulin</b> , infliximab, minocycline
Serum sickness-like eruption	<b>Morbiliform to urticarial</b> eruption that starts 1–3 wks after drug initiation; most commonly affects <b>kids</b> ; <b>edema of face/hands/feet</b> ; +/- arthralgias, arthritis, lymphadenopathy, fever; <b>lacks many elements of true serum sickness</b> (vasculitis, renal disease, hypocomplementemia, circulating immune complexes); self-limited Treatment options: long-acting H1-antihistamines +/- H2 antihistamine, NSAIDs, systemic steroids	<b>Cefaclor (#1)</b> >> other β-lactams, NSAIDs, minocycline, phenytoin
Symmetrical drug-related intertriginous and flexural exanthem (SDRIFE, “baboon syndrome”)	<b>Symmetric</b> eruption that p/w well-defined red plaques in <b>anogenital area</b> +/- other intertriginous/flexural sites after administration of <b>systemic med</b> (may be either first or repeated exposure); lack systemic symptoms (Note: SDRIFE and “baboon syndrome” variant of systemic ACD have similar clinical presentations and both have been termed “baboon syndrome”)	<b>β-lactams</b> (aminopenicillins and CSNs), <b>radiocontrast</b> , other antibiotics
Flagellate eruptions	<b>Bleomycin</b> : urticarial initially → later becomes hyperpigmented; occurs at sites of scratching <b>Raw shiitake mushroom</b> ingestion: more urticarial than bleomycin Other causes: adult onset Still’s disease, <b>dermatomyositis</b> , docetaxel	
Red man syndrome	Appears within 10 min of drug infusion; p/w <b>flushing of posterior neck</b> +/- face, upper trunk with associated pruritus and <b>hypotension</b> +/- angioedema; due to non-immunologic mast cell degranulation; Rx: ↓rate of infusion, pretreat with anti-histamines	<b>Vancomycin</b> (if infused too rapidly)
Radiation-induced EM	Has a <b>very specific clinical scenario</b> – occurs when phenytoin is given to neurosurgical pts undergoing whole brain radiation; p/w edema and red discoloration on <b>head at radiation ports</b> → develops into EM or SJS-like lesions within 2 days and <b>spreads downward</b> +/- mucosal involvement; histology: same as EM or SJS	<b>Phenytoin + radiation</b>

(Adapted from Tables 33.2, 21.13, 66.9, 67.3 and 71.8 in Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- **Third and fourth degree:** third (full thickness skin destroyed → ulcer → scar) and fourth (loss of skin and subcutaneous fat +/- underlying structures)
  - Grafting usually needed to help with function/contractures
  - May need to excise non-healing tissue
  - Silver impregnated dressings may help to ↓ infection risk
  - Diligent wound care and monitoring for infection are key
  - If > two thirds body involved = poor prognosis/↑mortality (women, infants, and toddlers)
  - For larger surface areas will need IV fluid resuscitation

### Erythema ab igne

- Thick **reticulated erythema** and/or pigmentation from chronic, non-burning, heat/infrared radiation exposure to a particular anatomic site
- F > M
- Classic sites and causes: shins (**space heaters**), lower back (**heating pad**), and anterior thighs (**laptop**)
- Possible ↑SCC risk

### Cold injuries

- **Acrocyanosis**
  - **Blue discoloration** of hands and/or feet +/- hyperhidrosis; ↑ with colder temperatures
    - **Young women** mainly
    - May be a/w butyl nitrite, interferon-α 2a, malignancy, and anorexia nervosa
  - Main DDx is **Raynaud's syndrome** (episodic; **red/white/blue** phases a/w cold; can → ulceration and distal fingertip resorption)
- **Pernio**
  - **Symmetric red-blue/purple macules/papules of acral skin** (toes/fingers most commonly) + burning/itching after cold or wet exposure
    - Ulceration may be seen
    - Histology: dense superficial and **deep PV** and **perieccrine** lymphocytic infiltrate + **dermal edema**
  - DDx includes chilblain lupus (exclude via serologic testing and/or biopsy) and blood dyscrasias (exclude via CBC w/ diff, cryoglobulins, cryofibrinogens, cold agglutinin, and SPEP/IF)
  - Treatment: warming measures (resolves in few weeks); **nifedipine** may be used
- **Frostbite**
  - Cool, blanched, anesthetic, and woody/hard skin → red/purple color (from hyperemia) + blisters + pain → desquamation/healing vs possible amputation
  - Pathogenesis: skin temperature drops below -2°C → vasoconstriction and occlusion → skin damage
  - Most common locations = **ears and nose**
  - Treat with warm (37–39°C) water bath **rapidly**

## Photodermatoses

### Sunburns and pigment darkening

- ↑UV exposure (UVB most commonly) → intense inflammation/erythema +/- blistering/edema (**peaks at 12–24 h with UVB**) → desquamation
  - Redness may take several days to fade
  - Severe cases may require hospitalization
  - Symptom relief with NSAIDs, corticosteroids, creams/lotions, and water intake
- Various forms of pigment darkening/tanning:
  - **Immediate pigment darkening:** within 10–20 mins of **UVA light** exposure; secondary to photooxidation of melanin + melanin redistribution within melanocytes
  - **Persistent pigment darkening:** brown coloration present >2 hrs after **UVA light** exposure, lasting 24 hrs; due to **oxidation of melanin**
  - **Delayed pigmentation/tanning:** develops over many days and lasts weeks to months; due to **UVB light** (mainly), resulting in ↑**melanin synthesis**

### Photoaging

- **Solar elastosis:** thickened, wrinkled, yellowish skin on chronically sun-damaged skin
  - **Cutis rhomboidalis nuchae** – solar elastosis variant affecting posterior neck with geometrically patterned leather-like wrinkled skin
- **Poikiloderma of Civatte:** reticular reddish-brown telangiectatic patches on lateral neck (central submental region spared)
- **Favre-Racouchot syndrome:** clusters of large open comedones on lateral/inferior periorbital area/temple + solar elastosis
- **Colloid milium:** 1–2 mm white-yellow subcutaneous papules, often grouped in sun-exposed regions of face
- **Erosive pustular dermatosis:** pustules + crusts + erosions on significantly photodamaged scalp of old, bald men
  - No consistently effective treatment; topical steroids or calcineurin inhibitors may be tried

### Polymorphous light eruption

- **Most common photosensitive dermatosis;** affects 5%–20% of Caucasians
- Erythematous, itchy papules, vesicles, or plaques (hence “polymorphous”) on sun-exposed areas (malar face, V of neck, outer arms, and dorsal hands); **arises 1–4 days after UVA** (> UVB > visible light) exposure
  - In ethnic skin, may see clusters of pinpoint papules resembling lichen nitidus
  - Juvenile spring eruption is a variant seen in young males aged 5–12 yo (**discussed in Pediatric Dermatology chapter**)
- Young F > M (3:1)
- Occurs in **spring/early summer**, particularly in northern latitudes
- Lesions last days to weeks
- Improves as summer proceeds (“**hardening**” effect)

- Etiology unknown, but felt to be delayed-type hypersensitivity reaction to UVR-induced neoantigens in skin
- MED phototesting may be normal or may be decreased to UVA and/or UVB
- Histology: **marked papillary dermal edema** + dense perivascular dermal lymphocytic inflammation
- Treatment:
  - **Photoprotection (first line):** broad-spectrum sunscreens that **block UVA (avobenzone, titanium dioxide, and zinc oxide)**, DermaGard film for windows
  - Others: phototherapy (prophylactic, in early spring), antimalarial prophylaxis and corticosteroids for flares (may use systemic steroids if severe)

## Hydroa vacciniforme – discussed in Pediatric Dermatology chapter

### Chronic actinic dermatitis

- Chronic, pruritic, eczematous eruption in **photodistributed areas**
  - Spares skin furrows, upper eyelids, nasolabial folds, postauricular, and finger webs
  - Over time may spread to non-sun-exposed areas
  - Over time, eruption becomes **lichenified/thickened**
- Seen in **men > 50 yo**, primarily in temperate climates; worsens in the summer
- **Phototesting positive to UVA, UVB, and/or visible light (UVA + UVB most common)**
- Unknown etiology – possibly allergic contact response to UV-damaged molecule secondary to UV-induced cutaneous immunosuppression or ↑immune reactivity
- Patch testing and photopatch testing may also be positive (especially *Compositae* or sunscreens)
- Treatment: photoprotection, avoid possible sensitizers, PUVA, topical, and systemic immunosuppressants; **severe UVB photosensitivity and ≥ two contact allergens are poor prognostic predictors**

## Actinic prurigo – discussed in Pediatric Dermatology chapter

### Solar urticaria

- Urticarial, itchy/burning, lesions appearing **within 30 minutes** in sun-exposed sites (especially upper chest and outer arms) after exposure to **visible light (#1 cause)** or UVA (#2)
  - Lesions resolve within 24 hrs
  - F > M; middle aged
  - May occur with **erythropoietic protoporphyria**
  - Severe attacks rarely: bronchospasm, syncope, and nausea
- Etiology unknown, but felt to be **type I hypersensitivity** reaction (i.e., skin chromophore absorbs a photon → transforms into an endogenous photoallergen → recognized by IgE)

- Treatment: **photoprotection, antihistamines** (high dose, non-sedating), phototherapy, and immunomodulators (IVIG and omalizumab)

## Porphyrias with cutaneous findings

- Cornerstone is diligent photoprotection with physical sunblock, avoidance of skin trauma, and good skin care
- Porphyria cutanea tarda
  - **Most common porphyria**
  - Due to ↓hepatic **uroporphyrinogen decarboxylase (UROD)** activity
    - Three types (I: familial, II: sporadic/acquired, III: normal UROD gene, but multiple affected family members)
      - ◆ **Type II (sporadic/acquired) form most common**
  - Skin findings (Fig. 3-79) include: skin fragility, vesicles, bullae, **erosions, milia, scarring, hyperpigmentation, and hypertrichosis** in photodistributed areas (especially dorsal hands/forearms)
    - **Classic photo is hemorrhagic blisters on dorsal hands (Fig. 3-79)**
  - Hepatomegaly and cirrhosis may be seen
  - Plasma fluorescence emission **peak at 620 nm**; ↑uroporphyrin III/↑heptaporphyrin/↑other porphyrins (including pentacarboxyporphyrin and coproporphyrin) in urine; ↑isocoproporphyrin/↑heptacarboxylporphyrin III in stool
  - Multifactorial disease with various associations/triggers (**alcohol abuse, estrogen, iron and hemochromatosis, hepatitis C, and HIV**)
  - Histology: **cell-poor subepidermal bulla w/ “festooning” of dermal papillae, “caterpillar bodies”** (pink BMZ material in blister cavity and epidermis)
  - DIF: IgG, IgM, fibrinogen, and C3 **linearly along BMZ and in superficial dermal vessels** (see thickened deposits around vessels)
  - Treatment: **avoid precipitating factors** (alcohol and estrogen), **photoprotection/sun avoidance**, treat



**Figure 3-79.** Porphyria cutanea tarda. Marked fragility with multiple hemorrhagic crusts, erosions, milia, and scars. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)



- underlying conditions (if any), **phlebotomy**, low dose hydroxychloroquine, and deferasirox
- **X-linked dominant protoporphyria**: presents similarly to EPP (with more frequent liver disease) and is due to a gain of function mutation in the *ALAS2* gene that encodes 5-ALA synthase
  - **Hepatoerythropoietic porphyria**
    - **Homozygous** mutation of uroporphyrinogen decarboxylase (**UROD**)
    - Laboratory: ↑zinc protoporphyrin in RBCs and plasma fluorescence emission peak at 620 nm; ↑uroporphyrin /↑coproporphyrin in urine and stool
    - Starts in **childhood/infancy** (Fig. 3-80) → scarring, sclerodermoid changes, photosensitivity to point of **mutilation**, hypertrichosis, milia, and vesicles/bullae/erosions/ulcers
    - Treatment: photoprotection, sun, and trauma avoidance
  - **Variegate porphyria**
    - AD mutation in **protoporphyrinogen oxidase** (located in mitochondria)
    - Rare – more common in **South Africa** and **Chile** due to founder effects
    - Skin findings similar to PCT +/- neurovisceral attacks
    - Laboratory: plasma fluorescence emission peak = 626 nm; ↑ALA/↑PBG/↑coproporphyrin in urine; ↑protoporphyrin IX/↑coproporphyrin III:I ratio (protoporphyrin > coproporphyrin) in stool
    - Treatment: avoid triggers (e.g., porphyrinogenic drugs, alcohol, and hormones); for acute porphyric attacks, supportive care in ICU with sufficient caloric supplementation, IV hemein or heme arginate infusion, and supportive medical treatments (β-blockers, narcotics, phenothiazines, gabapentin, and laxatives); LHRH or GHRH agonists, prophylactic hemein and cimetidine may help prevent future attacks
  - **Hereditary coproporphyria**
    - AD mutation in **coproporphyrinogen III oxidase** (located in mitochondria)
    - Acute attacks more common in women than men
    - **Neurovisceral attacks** + skin findings similar to PCT



**Figure 3-80.** Hepatoerythropoietic porphyria. Hypertrichosis and severe scarring are seen, resulting in a clinical appearance similar to congenital erythropoietic porphyria. Courtesy, José Mascaro, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Laboratory: ↑ALA/↑PBG in urine; ↑coproporphyrin III:I ratio (coproporphyrin III > protoporphyrin)
- Treatment is similar to VP
- **Congenital erythropoietic porphyria** (Gunther's disease)
  - AR deficiency of **uroporphyrinogen III synthetase (UROS)** → overproduction of uroporphyrin I and coporphyrin I in **erythrocytes, plasma, urine, and feces**
    - Also XLR mutation in *GATA1* (transcription factor that regulates expression of UROS)
  - Cutaneous features: photosensitivity with blistering, scarring, mutilating cutaneous deformity, sclerodermatous changes, hypertrichosis, dyschromia, and alopecia (Fig. 3-81)
  - **Red urine noted during infancy** due to ↑porphyrins, which are excited by visible light at **400–410 nm (Soret band)** and emit a red fluorescence
  - Splenomegaly, cholelithiasis, and hemolytic anemia
  - Pathologic fractures, osteopenia, vertebral compression, and contractures of fingers
  - Conjunctivitis and corneal scarring
  - **Erythrodontia** → teeth fluoresce under Wood's lamp examination
  - ↑urinary/erythrocyte uroporphyrin I; ↑urinary and fecal coproporphyrinogen I and uroporphyrinogen I
  - Treatment: strict photoprotection, hypertransfusions, and iron chelation such as with deferoxamine; splenectomy may be considered, use of **ascorbic acid** and **α-tocopherol** has been advocated; ocular lubricants, and allogeneic bone marrow transplantation
  - Poor prognosis for those with severe hematologic disease, or who present early unless treated with hematopoietic cell transplantation
- **Erythropoietic protoporphyria**
  - **Most common form of porphyria seen in children**
  - Caused by **ferrochelatase** mutations
    - AD and AR forms
  - Usually becomes symptomatic between 1–6 years of age
  - Manifests as burning/stinging/itching 5–30 mins post-sunlight exposure
  - Pruritic erythematous/edematous plaques that last 1–2 days post-sunlight exposure
  - Hypo-/hyperpigmentation, photoonycholysis



**Figure 3-81.** Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)



- Shallow linear pits may develop on the face, along with a papular eruption over the knuckles
- Hemolytic anemia and mild hypertriglyceridemia may be seen
- Cholelithiasis**; protoporphyrin accumulation in the liver may → hepatotoxicity and progressive hepatic dysfunction
- Treatment: strict photoprotection, **oral β-carotene** may be helpful in some patients, and hypertransfusion/plasmapheresis/exchange transfusion may be helpful in some patients; liver transplantation may be necessary with hepatic failure

## Mechanical injuries

- Callus**: keratotic broad-based areas secondary to habitual trauma/friction on feet (e.g., poorly fitting footwear, anatomic bone structure of foot, and physical activity)
- Corns**: smaller and more sharply defined than calluses, with two types (hard corn: firm w/ translucent central cores; soft corn: painful papules between toes)
  - DDx**: warts do not have translucent central core, have thrombosed capillaries/pinpoint bleeding with paring, and disrupt dermatoglyphics (unlike callus which has normal dermatoglyphics)
- Chondrodermatitis nodularis helices chronica**
  - Tender pink crusted papules on cartilaginous portions of helix and antihelix ear (upper helix #1 site in men, mid antihelix #1 in women)
  - Seen in middle aged and elderly patients
  - Histology: acanthosis and parakeratosis with **epidermal disruption/ulceration**; underlying dermis with reparative changes/ fibrosis, **necrotic cartilage** (appears pale or pink instead of normal blue-purple color)
  - Treatments: specially designed pillows, surgical methods, and IL steroid
- Piezogenic papules**: herniation of fat through fascia of lateral heels – best seen when patient is standing with weight placed on heel
- Traumatic auricular hematoma**: trauma to external ear → subperichondrial hematoma → **cauliflower ear** over time if not treated (hematoma organizes and develops fibrocartilage +/- calcification)
  - Usually seen in **wrestlers** as tender induration on upper anterior ear
  - Treatment = hematoma evacuation + recurrence prevention (e.g., via splint)

- Black heel (talon noir)**: cluster of black pinpoint macules on posterior heel(s)
  - Athletic trauma → rupture of superficial dermal vessels → hemoglobin in stratum corneum
- Acanthoma fissuratum**: firm skin-colored/red plaque on upper postauricular sulcus/upper lateral nose with groove running vertically through center of lesion; **due to poorly fitting eyeglass frames**

## 3.16 AMYLOIDOSES

- Group of disorders with extracellular amyloid deposition
  - Amyloid = fibril protein (various types including AL and AA) in a **cross-β-pleated sheet**
    - Histology = homogenous, eosinophilic, fissured masses that stain with **Congo red** and have **green birefringence with polarized light**
    - Amyloid also stains positively with **crystal violet, PAS, and thioflavin T**
      - AA amyloid (secondary systemic amyloid) loses Congo red affinity after exposure to potassium permanganate
- Divided into systemic primary, secondary, genetic (e.g., autoimmune syndromes and MEN2A, which are discussed in the **Pediatric Dermatology** chapter), hemodialysis-associated (β<sub>2</sub>-microglobulin) types, and localized (cutaneous, endocrine, and cerebral) types.
  - Localized cutaneous amyloidosis**
    - Three forms: **macular, lichen, and nodular** (Table 3-33) and (Fig. 3-82)
    - No great treatments – depending on depth, range from topicals to phototherapy/laser to surgery
    - More common in **Asians, Hispanics, and Middle Easterners**
  - Primary systemic** (AL – Ig light chain, usually λ subtype) amyloidosis
    - Can involve several organ systems (worst prognosis if cardiac involvement)
    - Mucocutaneous lesions in one third of patients
    - Due to **underlying plasma cell dyscrasia** (15% with myeloma)
    - Papules/nodules/plaques (waxy, translucent, and/or purpuric), ecchymosis/**pinch purpura** (eyelids, neck, anogenital, and axillae), **macroglossia** (see

Table 3-33. Cutaneous Amyloidoses

Type	Description	Derivation	Protein	Other Facts	Histology
Macular amyloidosis	Confluent or rippled ("salt and pepper"), pruritic, hyperpigmented patches ( <b>interscapular back</b> most commonly)	Keratinocyte tonofilaments (usually keratin 5)	Aker	Different but overlaps with notalgia paresthetica	Amyloid in papillary dermis
Lichen amyloidosis	Rippled, hyperpigmented, pruritic papules/plaques on extensor surfaces (esp. <b>shins</b> )	Keratinocyte tonofilaments (usually keratin 5)	Aker	Seen in <b>MEN 2A</b>	Amyloid in papillary dermis
Nodular amyloidosis	Pink to <b>yellow waxy nodules</b> and/or plaques	<b>Ig light chains</b>	AL	May be a/w Sjogren's, scleroderma and RA <b>Progression to systemic amyloidosis in 7%</b>	Amyloid in reticular dermis, subcutis, <b>vessel walls</b>



**Figure 3-82.** Lichen amyloidosis. Keratotic, hyperpigmented plaques on the legs. Insert: closer view of individual keratotic papules. Courtesy, St John's Institute of Dermatology. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

teeth indentations on sides of tongue), **carpal tunnel syndrome**, and **bullous amyloidosis** (rare)

- ◆ May have sclerodermoid presentation w/ alopecia and cutis verticis gyrata-like scalp changes
- Histology: **amyloid throughout dermis and subcutis, in sweat glands, and blood vessel walls**
- Check UPEP/SPEP and IFE
- Poor prognosis
- **Secondary systemic amyloidosis** (AA amyloidosis)
  - Sequela of severe **chronic inflammatory diseases** (e.g., ankylosing spondylitis, Tb, JIA, dystrophic EB, scleroderma, and autoinflammatory syndromes like Muckle-Wells)
  - SAA (serum amyloid A) protein is processed to AA amyloid in tissues
  - **Rare skin deposition**; usually involves kidneys, liver, spleen, adrenals, and heart
    - ◆ Of note, **amyloidosis in hemodialysis patients** has  $A\beta_2M$  amyloid ( $\beta_2$ -microglobulin) – usually no skin involvement, but may see subcutaneous nodules on lower back

### 3.17 NEURODERMATOLOGY AND PSYCHODERMATOLOGY

- Mediators of pruritus
  - C and A- $\delta$  nerve fibers in superficial skin produce **itch** sensation
  - **Histamine** produces pruritus via H1 receptor

- Other pruritogens: trypsin, serotonin, papain, kallikrein, bradykinin, substance P, VIP, and kallikrein
- Prostaglandins can exaggerate pruritus
- **Opiates** can produce pruritus via central and peripheral actions

### Internal causes of pruritus

- **Chronic kidney disease**
  - Localized or generalized **intractable, severe, paroxysmal pruritus** in 20%–80% of patients w/ CRI; **worst at night and 2 days post-hemodialysis**
  - Treatments: **NB-UVB**, emollients, and gabapentin; renal transplant is curative
- **Biliary pruritus**
  - Patients w/ **obstructive hepatitides, including carcinoma**
  - Generalized migratory pruritus not relieved by scratching; worse on hands, feet, and body areas covered by clothes and at night
  - Treat underlying hepatic disorder; some studies show improvement w/ **cholestyramine**, **ursodiol**, rifampin, naltrexone, naloxone, and thalidomide
- **Polycythemia vera**
  - 30%–50% of PCV patients have pruritus, **usually aquagenic** (severe pruritus in absence of skin changes, within minutes of water contact)
  - Pathogenesis: platelet aggregation causing serotonin and histamine release; mutation in JAK2 → constitutive activation and agonist hypersensitivity in basophils
  - Treatment: ASA, NB-UVB, PUVA, and oral antihistamines for pruritus; treatment of PCV
- **Malignancy**
  - Persistent, unexplained, intractable pruritus without primary skin lesion
  - a/w hematologic or biliary malignancies
  - Treatment: treat underlying malignancy; SSRIs, mirtazapine, and thalidomide
- **Endocrine**
  - Severe generalized pruritus (**hyperthyroidism**), generalized pruritus, or localized genital/perianal pruritus in **diabetes mellitus**
    - Localized pruritus of genitals is a/w poor glycemic control in women
  - Treatment: correct hyperthyroid state, improve glycemic control

### Pruritus ani

- Pruritus of anus and perianal skin (1%–5% population); **male >> female**
- Skin appearance: normal to severely irritated (erythema/crusting/lichenification, erosions/ulcerations)
- Pathogenesis:
  - **Primary pruritus ani**: pruritus in absence of cutaneous, anorectal, or colonic disorder; may be due to dietary factors, poor personal hygiene, or psychologic disorders

- **Secondary** pruritus ani: due to irritation from stool or hemorrhoids, primary cutaneous disorders, infectious or infestations, previous XRT, neoplasms, or contact allergy
- Treatment: reduce irritation w/ sitz baths, cool compresses, meticulous hygiene, mild topical steroids or topical calcineurin inhibitors, and treatment of underlying disorder

### Pruritus scroti/vulvae

- Acute or chronic pruritus of scrotum or vulva; worse at night; **lichenification** secondary to repeated rubbing/scratching
- Pathogenesis – acute: infections, allergic or irritant contact dermatitis; chronic: secondary to dermatoses, malignancy, atrophic vulvovaginitis, lumbosacral radiculopathy, irritation, or psychogenic (1%–7% patients)
- Treatment: specific to underlying etiology

### Scalp pruritus

- May be **primary** (lacks skin lesions; a/w anxiety and depression) or **secondary** to dermatoses (psoriasis, seborrheic dermatitis, and folliculitis)
- Treatment: emollients and topical steroids; tar or salicylic acid shampoos, and low dose doxepin

### Aquagenic pruritus and aquadynia

- Severe **pruritus** or **burning pain after water contact**, irrespective of water temperature; within 30 min of contact with **no visible skin changes**; lasts up to 2 hrs; spares head, palms/soles, and mucosae
- Pathogenesis: usually secondary to systemic disease (e.g., **polycythemia vera**) or other skin disorder
- Treatment: alkalization of bath water to pH 8, oral antihistamines, phototherapy, and capsaicin; clonidine and propranolol for aquadynia

### Drug-induced pruritus

- Chronic pruritus with or without skin eruption
- Common culprits: **opioids** (secondary to action on various opioid receptors in skin and centrally), chloroquine, and hydroxyethyl starch (volume expander injected into skin → direct stimulation of cutaneous nerves)
- Rx: discontinue inciting medication

### Lichen simplex chronicus

- Well-defined plaques w/ **lichenification**, hyperpigmentation, and varying erythema that are solitary or multiple and usually on **posterior neck**, occipital scalp, anogenital skin, **shins/ankles**, dorsal hands and feet, and forearms of older adults with xerosis, atopy, stasis, psychologic conditions, or pruritus secondary to systemic disease
  - Broader, thinner lesions than prurigo nodularis but w/ same **itch-scratch cycle** perpetuating the condition

- Rx: treat underlying systemic or psychiatric illness if present; **avoidance of scratching/rubbing**; topical/intralesional agents (corticosteroids and calcineurin inhibitors); topical antipruritics (menthol and pramoxine), antihistamines, and behavioral therapy

### Prurigo nodularis

- Multiple pruritic, **dome-shaped**, firm, hyperpigmented papulonodules that may have central scale/crust/erosion/ulceration distributed symmetrically on **extensor extremities** with sparing of mid-back (“**butterfly sign**”)
- Caused by chronic repetitive scratching/picking secondary to pruritic systemic or dermatologic disease or psychologic condition
- Most commonly in **middle aged adults** with underlying dermatologic/psychiatric disorder and occasionally in children with atopy
- Rx: **SSRIs/TCA**s for underlying psychologic condition, **doxepin**, MTX, thalidomide/lenalidomide, topical capsaicin, calcipotriene, liquid nitrogen, and cyclosporine

### Cutaneous manifestations of psychiatric illness or self-induction

#### Delusions of parasitosis

- Somatic delusional disorder; average onset 50–60 yo; close contacts may share delusion
- Younger patients: low socioeconomic status w/ history of substance abuse
- Older patients: higher socioeconomic status
- **Fixed false belief** that they are infested w/ parasites in absence of clinical findings; may describe sensations of biting, crawling, or stinging; “**matchbox sign**” (patient brings in bits of skin and other materials he/she believes are parasites)
- Rx: antipsychotic such as **pimozide** is classic treatment of choice (be aware of **QT prolongation** on EKG, extrapyramidal side effects, and drug-drug interactions); newer atypical antipsychotics (risperidone and olanzapine) appear effective w/ improved side-effect profile

#### Neurotic excoriations

- Excoriations in different stages of evolution with **geographic/angulated shapes**; favors extensor arms, scalp, face, upper back, and buttocks
- Caused by conscious, repetitive, and uncontrollable picking/scratching
  - Patients **admit to picking**, but cannot control behaviors
- Rx: **doxepin (ToC)**, SSRIs, behavior modification, behavioral and cognitive therapy, topical antipruritics, and wound care

#### Factitial dermatitis/dermatitis artefacta

- Patients self-inflict cutaneous lesions and **deny personal involvement**

- Geographic excoriations/erosions/ulcers within reach of hands
- Occurs in **adolescents/young adult females** who may work in healthcare fields or have personal disorders
- Rx: supportive wound and psychiatric care; antidepressant, anti-anxiety, or antipsychotic medications may be necessary

### Gardner-Diamond syndrome

- Patients traumatically induce lesions by various methods, causing sudden onset of **painful, swollen ecchymosis at sites of trauma**; affects any anatomic site, variable size, resolves within 2 weeks, and recurs
- Most often in women with underlying psychologic conditions
- Rx: very difficult, but antidepressants and psychotherapy can be beneficial

### Trichotillomania (discussed in Alopecia section)

### Body dysmorphic disorder

- Patients are **preoccupied by appearance** of their bodies and start obsessively checking in mirrors for perceived imperfections and may have **repeated cosmetic procedures**
- Typical areas of concern include face, hair, breasts, and genitalia
- Rx: SSRI for OCD variant and antipsychotics for delusional variant

### Cupping/coining

- **Cupping**: method of traditional Chinese medicine used to stimulate acupuncture points by placing burning cotton in a jar that is then placed on skin → creates a vacuum → results in **circular areas** of erythema and/or ecchymosis after removal
- **Coining**: technique used in Southeast Asia to improve circulation; involves rubbing oiled skin with a coin or spoon in symmetric, linear patterns that creates **patterned/linear ecchymosis**

### Other neurocutaneous dermatoses

### Scalp dysesthesia/burning scalp syndrome

- Diffuse burning pain/pruritus/numbness/tingling of scalp without primary skin lesions, usually found in **depressed/anxious middle aged to elderly women**
  - Secondary causes: seborrheic dermatitis, lichen planopilaris, contact dermatitis, folliculitis, dermatomyositis, and discoid lupus erythematosus
- Scalp is most frequent body region affected in correlation w/ stressful life events
- Rx: gabapentin, tricyclic antidepressants, and topical capsaicin

### Burning mouth syndrome

- **Burning mucosal pain** of the **anterior two thirds** of tongue, palate, and lower lip bilaterally (sparing buccal mucosa and floor of mouth) without primary lesions
- Middle aged to elderly adult females
- **Secondary causes must be excluded**: oral malignancy, xerostomia, contact dermatitis, medications, nutritional deficiencies, endocrinopathies, and psychiatric conditions
- Rx: antidepressants, benzodiazepines, gabapentin, antifungals, antibiotics, and “magic mouthwash” combinations

### Brachioradial pruritus

- Chronic intermittent pruritus or burning pain on **dorsolateral forearms/elbows** (overlying the location of brachioradialis muscle)
- May be secondary to **photosensitivity** or **cervical nerve root impingement** (many patients have prior back injuries)
- Rx: **treat cervical spinal impingement** if present, sun protection, topical capsaicin/pramoxine/amitriptyline/ketamine, gabapentin, physical therapy, and acupuncture

### Notalgia paresthetica

- Adults w/ focal, intense **pruritus**, pain, paresthesias, hyperesthesias of upper back (most commonly near **medial scapular borders**) +/- **hyperpigmented patches** secondary to chronic rubbing
- Etiology likely sensory neuropathy; up to 60% have **spinal impingement**
- Rx: topical capsaicin, topical corticosteroids or anesthetics, gabapentin, acupuncture, paravertebral block, and local botulinum toxin injection

### Meralgia paresthetica

- Localized numbness, burning, tingling, allodynia, or pruritus of **anterolateral thigh** secondary to **pressure on lateral femoral cutaneous nerve** as it passes under the inguinal ligament, often seen in middle aged obese males
- a/w **obesity**, pregnancy, prolonged sitting, **tight clothing**, and/or heavy wallets in pant pockets
- Rx: manage eliciting factors, focal nerve block, surgical decompression, topical capsaicin/corticosteroids/anesthetics, gabapentin, and acupuncture

### Complex regional pain syndrome/reflex sympathetic dystrophy

- Clinical presentation dependent on stage of disease
- Most common symptom is burning pain of upper limbs that is aggravated by movement or friction; affected **skin may become shiny, cold, and atrophic**
- Five major components: pain, edema, autonomic dysregulation, alterations in motor function, and **dystrophic changes**



- Damage to regional peripheral pain receptors → complicated signal cascade that eventually amplifies the pain response of CNS → clinical manifestations
- Rx: directed toward interrupting autonomic nervous system; often ineffective

### Trigeminal trophic syndrome

- Self-induced lesions of **central face** triggered by paresthesias/dysesthesias secondary to impingement or **damage of sensory portion of trigeminal nerve**
- May present as crusts or **ulcers of nasal ala** that can extend to cheek or upper lip w/ characteristic **sparing of nasal tip**
- Frequently occurs after treatment for trigeminal neuralgia w/ ablation of **Gasserian ganglion**; can also arise secondary to infection, stroke, and CNS tumors
- Rx: most successful is surgical repair with innervated skin flaps +/- various psychiatric medications, patient education, and protective barriers worn at night

### Familial dysautonomia/Riley-Day syndrome

- Neurodegenerative disease → various cutaneous and systemic findings: **defective lacrimation**, **absence of tongue papillae** with taste disturbance and **↑salivation**, impaired regulation of temperature and blood pressure, **↓pain sensation**, **absent tendon reflexes**, **hyperhidrosis**, **transient erythema** of trunk, vomiting crises, and **acrocyanosis of hands**
- Pathogenesis: **autosomal recessive** inheritance of **IKBKAP** (locus 9q31)
- Rx: supportive; 50% mortality by 30 yo due to respiratory issues

## 3.18 PALMOPLANTAR KERATODERMAS (PPKS)

- Hyperkeratosis of palmar and/or plantar skin
- Inherited (see [Pediatric Dermatology](#) chapter)
- Acquired PPKs
  - Keratoderma climactericum
    - Hyperkeratosis of pressure points on **heels in women >45 yo** (or younger women after oophorectomy)
    - Can be tender
  - Aquagenic PPK
    - Thick clear-white pebble-like palmar eruption **after water immersion** (quick onset)
    - Swelling and pain
    - F > M; usually starts during teenage years; a/w **cystic fibrosis**
    - Aluminum chloride can help
  - Keratolysis exfoliativa
    - Spots of exfoliation on palms and soles that spread centrifugally
    - Annular collarette of scale around exfoliation with no erythema
    - Likely represents a **mild form of eczema**

- Punctate keratosis of the palmar creases
  - 1–5 mm small plugs in creases of palms/fingers primarily in **African American patients**
- Punctate PPK (spiny keratoderma)
  - Typically <1 mm and usually multiple lesions
  - More common in blacks and men, and may be autosomal dominant
- Circumscribed palmar/plantar hypokeratosis
  - Well-defined pink, **circular depression** on palm (especially thenar and hypothenar) or sole (especially medial)
  - F > M; middle aged and older
  - Histology: **focally decreased stratum corneum/stratum granulosum**, underlying angioplasia
- PPK associations:
  - Malignancy:
    - PPK can occur in various carcinomas (e.g., lung and breast)
    - PPK can also occur in genetic cancer-causing disorders (e.g., Huriez syndrome (acral SCC), Howel-Evans syndrome (esophageal carcinoma))
    - **Arsenical keratoses** = focal keratotic papules on **palms/soles** → enlarge, ↑number, spread → ulceration and SCC
      - ◆ Arise >10 yrs after arsenic ingestion
  - Hypothyroidism: typically with myxedema of hypothyroidism; resolves with therapy
- Treatment: various keratolytic agents (e.g., ammonium lactate, urea, etc.); CO<sub>2</sub> laser

## 3.19 NUTRITIONAL DISORDERS IN DERMATOLOGY

- Can occur for a variety of reasons (inadequate intake, concurrent illnesses, problems with metabolism)
- Protein-energy malnutrition
  - Kwashiorkor: **↓protein intake** for at least several weeks (e.g., primarily rice diet)
    - Cutaneous findings:
      - ◆ **Dyschromia**
      - ◆ Hypopigmentation following trauma
      - ◆ Desquamation/erosion of skin (“**peeling/flaky paint**” appearance; most common finding on exam)
      - ◆ Bands of light and dark hair discoloration (“**flag sign**”) and sparse/dry/brittle hair
      - ◆ Compromised wound healing with ulceration and erosion
      - ◆ **Edema/anasarca**
      - ◆ Secondary infections
  - Marasmus: **↓energy/calorie intake** for months to years
    - Cutaneous findings:
      - ◆ **Thin, dry, lax, pale, and wrinkled/loose skin**
      - ◆ Lanugo-like hair
      - ◆ Purpura
      - ◆ Follicular hyperkeratosis
      - ◆ Impaired hair and nail growth
      - ◆ Emaciated (“**monkey facies**” – **↓buccal fat pads**)

- **Essential fatty acid deficiency:**
  - Secondary to malnutrition; other issues → fat malabsorption, parenteral nutrition w/o lipids, and **nephrotic syndrome**
  - Cutaneous findings: dry, rough, and scaly skin; erosions in flexures and rash similar to biotin and zinc deficiencies; alopecia w/ light colored hair; secondary infections
  - **↓linoleic, linolenic, and arachidonic acids**
  - **↑palmitoleic, oleic, and 5,8,11-eicosatrienoic acids**
- **Vitamin excesses and deficiencies**
  - See [Table 3-34](#) for specific vitamin abnormalities

**Table 3-34.** Vitamin Deficiencies and Excesses

Vitamin	Cutaneous Findings	Deficiency	Excess	Interesting Boards Facts
Vitamin A	<b>Phrynodema (keratotic follicular papules resembling toadskin)</b> , blindness, xerophthalmia		Desquamation, xerosis, cheilitis, epistaxis, dermatitis, alopecia ( <b>think of SEs with systemic retinoids</b> )	
Beta-carotene			<b>Carotenemia</b> and carotenoderma (yellow discoloration best seen on palms/soles and central face)	Can see in <b>diabetes, nephrotic syndrome, and hypothyroidism</b>
Biotin	Alopecia, <b>rash similar to zinc deficiency</b> (e.g., periorificial dermatitis)			Infantile type due to biotinidase defect; neonatal type due to holocarboxylase synthetase defects Acquired biotin deficiency: 1) diet rich in raw egg whites, which contain <b>avidin</b> (glycoprotein that complexes with and inactivates biotin), 2) parenteral nutrition lacking biotin, and 3) certain anticonvulsants (e.g., phenytoin, carbamazepine)
Selenium	<b>Hypopigmentation</b> of skin/hair, leukonychia, xerosis		Dermatitis, alopecia, abnormal nails	
Vitamin B1 (thiamine)	Glossitis, edema			
Vitamin B2 (riboflavin)	<b>Oral-ocular-genital syndrome</b> (cheilitis, angular stomatitis, seborrheic dermatitis-like rash, tongue atrophy/glossitis, genital and perinasal dermatitis)			Can be seen in breastfed infants of mothers who are deficient in riboflavin
Vitamin B3 (niacin)	<b>Pellagra</b> "Dermatosis" = <b>Casal's necklace</b> (upper chest/neck), <b>cheilitis/glossitis</b> , <b>photosensitivity</b> (esp. dorsal hands), perineal rash Plus other three Ds: <b>diarrhea, dementia, and death</b>		<b>Flushing</b> , pruritus, acanthosis nigricans	<b>Causes of deficiency:</b> <b>Hartnup dz</b> , alcoholism, <b>carcinoid syndrome</b> , <b>isoniazid</b> , 5-FU, <b>azathioprine</b> , anorexia, malabsorption syndromes
Vitamin B6 (pyridoxine)	<b>Seborrheic dermatitis-like</b> rash, angular cheilitis, intertrigo, glossitis		Photosensitivity	Highest risk of deficiency in <b>alcoholics</b>
Vitamin B9 (folic acid)	Hyperpigmentation (esp. hands, nails, face, palmar creases, intertriginous regions; oral sites can be involved), glossitis, angular cheilitis, hair depigmentation (cannities)			Goat milk diet can predispose
Vitamin B12 (cobalamin)	Similar to folic acid cutaneous SEs			Vitamin B12 deficiency may → <b>neurologic sequelae</b> , (not typically seen in folic acid deficiency) Malabsorptive states are a common cause
Vitamin C (ascorbic acid)	<b>Scurvy:</b> corkscrew hairs, perifollicular hemorrhage/hyperkeratosis (first cutaneous sign), hemorrhagic gingivitis, splinter hemorrhage of nails			
Vitamin D	<b>Alopecia</b>		Hypervitaminosis D	
Vitamin E			<b>Petechiae, ecchymoses</b>	
Vitamin K	<b>Purpura, ecchymoses, hemorrhage</b>			Antibiotics decrease <b>gut bacteria responsible for vitamin K production</b> → caution in pts on warfarin, as INR may become dangerously high
Zinc	<b>Perioral, perianal, and acral erosions;</b> erythema and crust <b>Alopecia</b> , paronychia, onychodystrophy, stomatitis, secondary infections <b>Classic triad</b> (dermatitis, diarrhea, depression) <b>seen in only 20%</b>			Deficiency can be inherited in AR pattern ( <b>acrodermatitis enteropathica</b> , mutation in <b>SLC39A4</b> gene) Risk factors for acquired deficiency = <b>alcoholism</b> , vegan diets, anorexia, HIV, certain drugs (e.g., penicillamine) See <b>low alkaline phosphatase</b> serum levels in zinc deficiency

- Pathology (pellagra, acrodermatitis enteropathica, acquired zinc deficiency, and glucagonoma): **pallor of top one third of epidermis +/- psoriasiform epidermal changes**
- **Anorexia nervosa**: may see **lanugo-like hair**
- **Bulimia nervosa**: may see **calluses/scars on knuckles/ dorsal hands (Russell's sign)**, enlarged salivary glands, and **erosion of tooth enamel**

### 3.20 DEPOSITIONAL AND CALCIFICATION DISORDERS NOT DISCUSSED ELSEWHERE (TABLE 3-35)

### 3.21 ULCERS (TABLE 3-36)

- Wound with loss of epidermis + dermis
- Various causes and types – important to look for clinical clues and order appropriate laboratory workup

### 3.22 VASCULITIDES, VASCULOPATHIES, AND OTHER VASCULAR DISORDERS

- Vasculitides are divided primarily according to vessel size that is targeted (Table 3-37)

**Table 3-35.** Depositional and Calcification Disorders Not Previously Discussed

Disorder	Histopathology	Clinical Findings	Pearls
Gout	Amorphous material with <b>needle-like clefts</b> in dermis Giant cells around material Negative birefringence	<b>Monosodium urate</b> crystals in tissue → gouty arthritis ( <b>first MTP joint most common</b> ), nephrolithiasis/ renal impairment, and gouty tophi (firm white/ yellow subcutaneous nodules) M > F, middle-aged Risk factors: <b>obesity, alcohol</b> , renal issues, diuretic meds <b>Gouty tophi most common on ear helix</b> and skin overlying small joints ( <b>fingers, toes</b> ); <10% pts get them	<b>Ethanol</b> is best preservative Diagnosis classically made by aspirating inflamed joint in acute arthritis → urate crystals in joint fluid Crystals stain black with 20% silver nitrate Treatment options: NSAIDs, <b>cocaine</b> , <b>allopurinol, febuxostat</b> DDx is pseudogout (deposition of <b>calcium pyrophosphate</b> crystals in joint and soft tissue) which can → tophaceous pseudogout
Colloid milium	Amorphous <b>homogenous pink nodular material</b> in superficial dermis +/- clefts Grenz zone <b>Solar elastosis</b> seen deep to nodules in adult form	<u>Adult type</u> (most common): pts usually middle-aged or older and <b>severely photodamaged</b> , M > F; multiple translucent yellowish papules in photo-exposed areas <u>Other types</u> : <b>juvenile</b> , pigmented (in setting of hydroquinone), nodular colloid degeneration	<b>Stains like amyloid</b> (congo red, thioflavin T, and crystal violet positive) PAS+
Dystrophic calcification	See appropriate sections	<u>ALCTD</u> : most commonly seen in <b>CREST</b> and <b>childhood DM</b> ; in DM, can → calcinosis universalis (severe form) <u>Panniculitis</u> : lobular, particularly <b>pancreatic panniculitis</b> , subcutaneous fat necrosis of the newborn, lupus profundus <u>Genodermatoses</u> : <b>PXE</b> (calcification of dermal elastic fibers), Ehlers-Danlos syndrome, PCT (longstanding) <u>Infections</u> : <i>Onchocera volvulus</i> and <i>Taenia solium</i> <u>Neoplasms</u> : <b>pilomatricomas (75%)</b> , BCCs, epidermal/ pilar cysts	
Metastatic calcification	<b>Calciophylaxis</b> : perivascular and intravascular calcium in vessels of SQ fat → thrombotic vasculopathy	<u>Clinical</u> : violaceous reticulated patches (livedo) + subcutaneous nodules → <b>painful</b> necrotic, purpuric ulcers/bullae; F > M; RFs: obesity, DM2, poor nutrition; <b>high mortality; check protein C activity/function</b> <u>Histology</u> : <b>thrombotic vasculopathy + vascular calcification</b> + necrosis of skin/soft tissue <u>Treatment</u> : low calcium <b>dialysis</b> , phosphate binders, <b>STS</b> , TPA, parathyroidectomy, surgical debridement, management of tissue infections	<b>Chronic renal failure</b> : #1 cause of metastatic calcification; due to ↓PO4-clearance, ↓1-α hydroxylation D3, ↓Ca++ absorption, 2° hyperparathyroidism Other causes of metastatic calcification: <b>milk-alkali syndrome</b> and <b>hypervitaminosis D</b>
Idiopathic calcification	Idiopathic calcified nodules of the <b>scrotum</b> : may see calcification in the setting of an epidermal cyst within scrotal skin	<b>Idiopathic calcified nodules of the scrotum</b> : multiple white small nodules of scrotum <b>Tumor calcinosis</b> : large painful calcium-phosphate subcutaneous nodules around joints → ulceration	Other causes include milia-like calcinosis (typically on dorsal hands/face in Down syndrome) and subepidermal calcified nodule
Osteoma cutis	Bone formation within dermis/SQ	<u>Genetic causes</u> : fibrodysplasia ossificans progressiva (process is endochondral; AD; mutation in ACVR1 gene which encodes activin A receptor; may have malformed great toes), progressive osseous heteroplasia, plate-like osteoma cutis, <b>Albright hereditary osteodystrophy</b> <b>Miliary osteomas of the face</b> : white-skin colored tiny papules on faces of adults, common; <b>a/w prior acne and TCN</b>	

**Table 3-36.** Key Features of Cutaneous Ulcers

Ulcer Types	Clinical Presentation	Useful Pearls
Venous	Irregular borders with shallow yellow fibrinous base Classically above <b>medial malleolus</b> (2° to Cockett's perforating veins) Usually in background of <b>venous stasis</b> changes (brown hemosiderin deposits + pinpoint purpura, LDS, edema) and varicosities	RFs: ↑age, F > M, obesity, pregnancy, prolonged standing, ↑height Due to venous HTN and insufficiency duplex U/S +/- venography may help characterize dz Treatment: moisture/occlusion, debridement, dressings (create moist environment but absorb excess exudate), treatment of infection, compression (do NOT use in arterial insufficiency pts), negative pressure therapy, manual lymphatic drainage, pentoxifylline, ASA, G-CSF
Lymphedema	Classically starts as pitting edema of dorsal foot → moves to leg Skin changes: induration, ulceration, 2° infection <b>Elephantiasis nostras verrucosa</b> : chronic lymphedema of feet/legs → fibrosis of dermis and subcutis → verrucous, hyperkeratotic, cobblestone-like, papillomatous appearance	Due to ↑ interstitial lymph fluid due to poor drainage 1° (e.g., Nonne-Milroy dz, Meige dz, lymphedema tarda) vs 2° (malignancy, radiation, LN dissection, CVI, recurrent cellulitis, obesity, filariasis)
Arterial (peripheral arterial dz)	Painful ulcer w/ well-defined borders with round, <b>"punched out"</b> dry, necrotic base classically at pressure points (e.g., <b>lateral malleolus</b> , first and fifth metatarsal heads) usually in background of <b>atrophic skin w/↓hair</b> claudication	<b>↓pedal pulses</b> w/ ↑capillary refill time and pallor w/ elevation <b>Diagnosis via ABLs</b> ; may need CTA, MRA, invasive digital subtraction angiography Due to lack of blood perfusion (peripheral arterial dz) RFs: tobacco, DM2, HTN, hyperhomocysteinemia, HLD Do NOT use VAC treatment or sharp debridement May need surgical reconstruction and/or <b>angioplasty</b>
Diabetic/neuropathic ("mal perforans")	"Punched out," smelly, <b>moist base with callused borders</b> Classically at <b>pressure points</b> (e.g., metatarsal heads, great toes, heels) Usually in setting of <b>peripheral neuropathy</b> +/- foot deformity (e.g., hammer toes)	May have underlying <b>osteomyelitis</b> (MRI best for dx) which may require bone bx/cx 15% of DM pts with foot ulcer → lower extremity amputation Treatments: <b>off-loading measures</b> (e.g., total contact casting, therapeutic shoes), wound healing measures (e.g., debridement), treatment of infection, hyperbaric oxygen, negative pressure therapy, exogenous growth factors (e.g., becaplermin gel), skin substitutes, dressings, G-CSF
Decubitus/pressure	Ulcer due to prolonged pressure from ↓ambulation/mobility → pressure to soft tissue from bony prominence and external surface Common sites: <b>sacrum</b> , heel, ischial tuberosities, greater trochanters, malleoli (lateral > medial) <b>Four stages</b> : I) non-blanchable erythema; II) skin loss of epidermis +/- dermis = erosion/shallow ulcer; III) skin loss + subcutis damage, but not fascia; and IV) tissue necrosis to muscle, bone or supporting structures	RFs: immobility, sensory deficit, poor nutrition, circulation issues Treatment: relief of pressure (e.g., position changes, support surfaces like foam wedges), good wound care Stage IV ulcers will likely need surgical treatment
Diffuse dermal angiomatosis	Violaceous/erythematous patches/plaques with ulceration on legs, <b>breasts</b> , forearms	Strongly a/w <b>vascular atherosclerosis</b> and <b>smoking</b> May need surgical intervention Isotretinoin recently described as treatment option
Arteriosclerotic ulcer of Martorell	<b>Painful</b> red blister → blue purpuric lesion → ulceration; ulceration is preceded by pigmented pretibial patches Anterior or medial <b>lower leg</b> Usually superficial ulcer w/ necrotic base and violaceous-erythematous edges, but may be deep and enlarging	Women 50–70 yo Poor healing and slow wound healing Typically a/w <b>HTN</b> Histology: impressive thickening of arteriole media and intima, +/- hyalinosis/ <b>calcinosis of media</b> , +/- periarteritis, +/- endarterial proliferation Treatment involves multiple modalities (e.g., VAC, HTN control, compression stockings)
Hematologic causes		Anemia, particularly hemoglobinopathies Hematologic malignancy associations: pyoderma gangrenosum, vasculitis, type I cryoglobulinemia Clotting abnormalities: factor V Leiden deficiency, protein C/S deficiency, anti-thrombin III deficiency, prothrombin G20210A mutation, APLS, hyperhomocysteinemia, plasminogen activator inhibitor deficiency/increase
Inflammatory		Consider vasculitis, PAN, RA/Felty's syndrome, pyoderma gangrenosum and necrobiosis lipoidica, Behcet's – lower extremity common site in aforementioned Ulcerative LP, ulcerative sarcoid, livedoid vasculopathy Consider panniculitides (pancreatic, α <sub>1</sub> -antitrypsin, erythema induratum)
Infectious		When suspected, culture broadly to r/o bacterial (e.g., anthrax), mycobacterial, viral (esp. <b>HSV</b> ), fungal, parasitic (acanthamoeba, amebiasis)
Neoplastic		Almost all cutaneous malignancies can → ulcer ( <b>SCC</b> most common, but also BCC, lymphomas, Kaposi's, angiosarcoma) <b>SCC can develop in chronic ulcers, scars, sites of chronic inflammation</b> (e.g., in hidradenitis suppurative or LS&A)
Metabolic		Ulcers can occur in depositional disorders (e.g., calcinosis cutis, gout) adjacent to joints, and higher fat areas in disorders like calciphylaxis

Continued



**Table 3-36.** Key Features of Cutaneous Ulcers—cont'd

Ulcer Types	Clinical Presentation	Useful Pearls
Genetic		Ulcers can be seen in <b>Adams-Oliver syndrome</b> (from aplasia cutis on scalp), <b>prolidase deficiency</b> (leg ulcers), familial tumor calcinosis, Werner syndrome (leg ulcers), Flynn-Aird syndrome, <b>Klinefelter syndrome</b> (leg ulcers)
Drugs		<b>Hydroxyurea</b> is a common culprit (malleolus, tibial crest; painful) other culprits are <b>interferon</b> (injection sites), <b>MTX in psoriasis pts</b> , anticoagulants (warfarin (2° to acquired protein C deficiency) and heparin necrosis (2° to HIT))
Other		Dermatitis artefacta, <b>illegal drug use</b> , burns, frostbite, radiation-induced, chemical etching

*\*Vasculitis and vaso-occlusive discussed in [Vasulitides](#), [Vasculopathies](#), and [Other Vascular Disorders](#) section*

**Table 3-37.** Categories of Vasculitis by Vessel Size

	Clinical Features	Examples
Small vessel vasculitis	<b>Palpable purpura</b> Petechiae Vesicles Pustules	Henoch-Schonlein purpura Acute hemorrhagic edema of infancy Urticarial vasculitis Erythema elevatum diutinum Granuloma faciale Secondary vasculitis Drug Infection Malignancy Autoimmune
Mixed small and medium vessel vasculitis	Mixture of features from small and medium vessel vasculitis	Mixed cryoglobulinemia Types II and III ANCA-associated: Microscopic polyangiitis Wegener's granulomatosis Churg-Strauss syndrome
Medium vessel vasculitis	<b>Livido reticularis</b> Retiform purpura Ulcers <b>Subcutaneous nodules</b>	Polyarteritis nodosa Kawasaki disease
Large vessel vasculitis	Specific per disease <u>Temporal arteritis:</u> erythematous tender nodules or ulceration on the frontotemporal scalp <u>Takayasu's arteritis:</u> erythematous subcutaneous nodules, PG-like lesions on LE > UE	Temporal arteritis Takayasu's arteritis

**Table 3-38.** Triggers of Cutaneous Small Vessel Vasculitis

Triggers	Examples
<b>Primary cutaneous small vessel vasculitis</b>	
Idiopathic (50%)	
<b>Secondary cutaneous small vessel vasculitis</b>	
Infection (15%–20%)	Bacterial: <b>group A β-hemolytic Streptococci</b> , <i>Staphylococcus aureus</i> , <i>Chlamydia</i> , <i>Neisseria</i> , <i>Mycobacterium</i> Viral: <b>hepatitis C</b> > B >> A, HIV Fungal/yeast: <i>Candida</i>
Inflammatory disorders (15%–20%): can present as a small and/or medium vessel vasculitis	Autoimmune CTD including: SLE, Sjogren's, RA >> Dermatomyositis, Scleroderma, Polychondritis IBD Behcet's disease
Drug (10%–15%): onset is 1–3 wks after drug initiation, third most common cutaneous drug eruption (2%)	<u>Most common:</u> Antibiotics: <b>β-lactams</b> (penicillin, cephalosporins), <b>sulfonamides</b> , minocycline, quinolones Antiinflammatory: <b>NSAIDs</b> , COX-2 inhibitors <u>Other culprits:</u> Leukotriene inhibitors Anti-thyroid: propylthiouracil Anti-hypertensives: thiazides, hydralazine Biologics: <b>TNF-α inhibitors</b> , MTX, Rituximab Hormonal: OCP's G-CSF Retinoid: isotretinoin <b>Levamisole-tainted cocaine</b> Allopurinol Radiocontrast media
Neoplasm (<5%)	<u>Most common:</u> Hematologic malignancy (Multiple myeloma Monoclonal gammopathies T-cell leukemia, MF, AML, CML Diffuse large cell leukemia Hairy cell leukemia) <u>Less common:</u> Solid organ (GU: prostate cancer, renal cancer GI: colon cancer)
Other	Thrombotic Embolic Cryoglobulinemia

## Cutaneous small vessel vasculitis

### Epidemiology

- Adults > children

### Pathophysiology

- Immune complex deposition in post-capillary venules → activates complement → neutrophilic inflammatory response → vessel damage, hemorrhage, and tissue ischemia
  - Fibrinoid necrosis of blood vessels arises via lysosomal enzymes (collagenases and elastases) and reactive oxidative species
- Various triggers exist ([Table 3-38](#))

### Clinical presentation

- Crops of partially blanchable, **symmetric, palpable purpura** on the **lower extremities**, dependent areas, and under tight clothing
  - Other manifestations: erythematous papules, urticaria, vesicles, pustules, and livedo reticularis

- Rarely occurs on the face, palms, soles, or mucous membranes
- Timing: appears 7–10 days after exposure and resolves within 3–4 weeks with transient hyperpigmentation and/or atrophy
- Cutaneous symptoms: asymptomatic, pruritus, burning, or pain
- Systemic symptoms: fever, malaise, arthralgias, myalgias, and GI/GU symptoms
  - If any are present → consider systemic vasculitis!
- Prognosis: 10% will have chronic and relapsing course

### Pathology

- H&E biopsy best within 18–48 hrs; DIF best even earlier (within 8–24 hrs)
  - After 48 hrs, pathology is non-specific and may show mononuclear cells rather than neutrophils
- Perivascular **neutrophilic infiltrate (w/ leukocytoclasia)** centered around post-capillary venules w/ **fibrinoid necrosis of vessel walls** and endothelial swelling, and **RBC extravasation**
  - Concomitant involvement of the deeper larger vessels → suggests systemic vasculitis
- DIF: 80% w/ **perivascular C3 and IgM**

### Laboratory testing

- ↑ESR suggestive of systemic disease
- Significant complement consumption is suggestive of more extensive or systemic disease
- If systemic disease is suspected, evaluate as per [Table 3-39](#)

**Table 3-39.** Evaluating for Systemic Vasculitis

General Workup	If There Is No Concern for Systemic Involvement:
	CBC [eosinophilia in CSS], BMP [↑Cr], ↑ESR (>40 mm/h), ↑LFT's, UA [hematuria/proteinuria]
Extensive Workup	If There Is Concern for Systemic Involvement Consider General Workup Plus:
GI	Stool guaiac [+/- melena in HSP]
Renal	Serial UAs [hematuria, proteinuria]
Infectious	Hepatitis B and C HIV ASO titer (if +), consider streptococcal infection) Abnormal CXR (infiltrates, opacities) Consider TTE and blood cultures in a patient with high fever or heart murmurs Consider other cultures based on history
Inflammatory	↑ESR ↑CRP (↑ in infection and autoimmune disease) ANA RF (if +) consider Sjogren's, Rheumatoid arthritis, cryoglobulinemia) C3, C4, CH50, C1q (WNL in NUV; ↓C3/C4/C1q in HUV, SLE, other autoimmune vasculitides, atheroembolization) ANCA ((+)c-ANCA in WG; (+)p-ANCA in MPA, CSS, PAN) Anti-phospholipid antibodies ((+) in APLS)
Neoplastic	SPEP/UPEP (if +) consider hematologic malignancy) CXR (nodules or masses suggestive of malignancy) Abnormal peripheral blood smear
Other	Cryoglobulins (if +), consider cryoglobulinemia) Immunoglobulins (IgA(+) in HSP, IgE(+) in CSS)

### Treatment

- Depends of severity of disease ([Table 3-40](#))

### Key testing facts

- Common presentation is palpable purpura on the lower extremities

## Subtypes of cutaneous small vessel vasculitis

### Henoch-Schonlein purpura (HSP)

#### Epidemiology

- **Most common pediatric vasculitis**
- **90% of cases occur in children <10 yo** with male predominance
- Seasonal variation, with winter predominance

#### Pathophysiology

- **IgA vascular deposition** in small blood vessels results in:
  - Activation of several cytokines
  - Neutrophil activation of nitric oxide and ROS
- Triggers:
  - Occurs 1–2 weeks after a **URI or Streptococcus** infection
    - Other infections: *Bartonella henselae*, Parvovirus B19, *S. aureus*, *H. pylori*, and Coxsackievirus
  - Drug exposure reported in a minority of patients

#### Clinical presentation

- Tetrad:
  - Skin: palpable purpura on the **buttocks** and lower extremities (100%)
  - Musculoskeletal: **arthralgias** (75%); arthritis of the knees and ankles

**Table 3-40.** Treatment Approach for CSVV

Severity of Disease	
Mild	Supportive measures: <b>90% will have spontaneous resolution</b> , 10% will have a chronic course Remove suspected meds Leg elevation and compression stockings NSAIDs for arthralgias is controversial H1 blockers, H2 blockers Topical steroids
Chronic or severe	Colchicine (0.6 mg, 2–3x/day) Dapsone (100–200 mg/day) Combination of <b>colchicine + dapsone</b> or colchicine + pentoxifylline is more efficacious than monotherapy
Severe ulcerating	Oral <b>prednisone</b> (0.5–1 mg/kg with a 4–6 wk taper) Can add immunosuppressive agents including: Azathioprine (1–2 mg/kg a day) Mycophenylate mofetil (up to 2g daily) Cyclophosphamide (1–2 mg/kg a day) Cyclosporine (2.5–5 mg/kg a day) IVIg (in an immunodeficient patient) Plasmapheresis (in refractory cases)

- GI: colicky abdominal pain (65%), diarrhea, +/- melena; hematochezia (20%)
- Renal (40%–50%): hematuria w/ risk of nephritis, ESRF (1%–3%)

#### Key features of adult HSP

- More likely to have aggressive course with diarrhea and **chronic renal insufficiency**
- Adults who p/w fever, ↑ESR, and **purpura above the waist** are more likely to have **IgA glomerulonephritis**
- a/w solid organ neoplasms (especially lung cancer) > hematologic neoplasms
- More frequent vesicubullous lesions and cutaneous necrosis (60%)
- Prognosis: recurs in up to 40%

#### Key features of childhood HSP

- Severe renal disease in 5%–7%
- Abdominal pain is a significant predictor of nephritis

#### Treatment:

- First line: supportive measures (self-limited disease and resolves in weeks to months)
  - Add prednisone +/- azathioprine or cyclosporine if abdominal pain, arthritis, or severe nephritis
    - Controversial if prednisone is preventative of renal disease (Cochrane review did **not** show benefit)
  - Dapsone shortens duration and helps with skin findings
  - Ranitidine decreases duration and severity of abdominal pain
  - IVIG considered if rapidly progressive glomerulonephritis

#### Laboratory testing: see CSVV section

- DIF shows IgA in blood vessel walls
- Long term f/u with serial UAs required (hematuria, proteinuria, and abnormal creatinine)
- Guaiac if abdominal pain or suspect GI bleed

#### Pathology:

- LCV
- DIF with IgA deposits, C3, and fibrin in dermal small blood vessels
- Rate of renal disease is greater if there are **no eosinophils** on skin biopsy

### Acute hemorrhagic edema of infancy

#### Epidemiology

- Occurs in children <3 yo
- 70% are boys

#### Pathophysiology

- Immune complex deposition in small blood vessels
- Triggers: (Table 3-41)

#### Clinical presentation

- Large **annular or targetoid/cockade**, edematous, hemorrhagic plaques on the head (cheeks and ears) and upper extremities (Fig. 3-83)

**Table 3-41.** Triggers for Acute Hemorrhagic Edema of Infancy

Triggers	
Infection: viral or bacterial	URI: adenovirus, coxsackievirus, EBV Diarrheal illness: hepatitis A, campylobacter, rotavirus UTI: <i>E. coli</i> Other: HSV, VZV
Drug	Antibiotics: $\beta$ -lactams, TMP/SMX Analgesic: NSAIDs, acetaminophen Vaccination



**Figure 3-83.** Acute hemorrhagic edema; typical large annular hemorrhagic plaques. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- Tender non-pitting acrofacial edema
- **Not ill-appearing**, but may be febrile
- Prognosis: resolves in 1 to 3 weeks

#### Pathology

- LCV
- DIF can have IgA deposits

#### Treatment

- Supportive with anti-histamines; resolves spontaneously in 1 to 3 weeks

### Urticarial vasculitis

- NUV (70%–80%): normocomplementemic urticarial vasculitis
  - Skin-limited and **idiopathic**
- HUV (20%–30%): hypocomplementemic vasculitis
  - Highly a/w systemic disease

#### Epidemiology

- **Females >50 yo** most commonly affected, especially in HUV (same demographics as AI-CTDs)

**Pathophysiology**

- Complement and immune complex deposition in blood vessel wall and activation of the complement cascade
  - Hypocomplementemic form: **IgG antibodies bind C1q → reduced serum levels of C1q**
- Causative agents: often idiopathic, but multiple triggers may play role (Table 3-42)

**Clinical presentation**

- **Painful/burning** urticarial lesions **lasting >24 hrs** (vs < 24 hrs for normal urticaria) on trunk and LE; resolves w/ **hyperpigmentation or purpura**; may have concomitant angioedema
- Recurrent episodes lasting months to years
- Systemic findings (more common in HUV) are highlighted in Table 3-43

**Pathology**

- LCV (often subtle in degree)
- Diffuse interstitial neutrophils seen more commonly in HUV and may be a/w SLE
- DIF: 70% perivascular Igs and C3, but a lupus band (granular Ig or C3 along the BMZ) increases the risk for SLE in HUV patients

**Laboratory testing**

- NUV: same as CSVV
- HUV: ↓CH50, C3 and C4; **anti-C1Q Ab** (~100% of HUV patients) and ↑ESR
  - Check ANA given strong association of HUV with SLE (up to 50%)

**Table 3-42.** Causes of Urticarial Vasculitis

<b>Idiopathic</b>	
Autoimmune disease	<b>SLE (associated w/ HUV)</b> <b>Sjogren's</b>
Infection – viral	Hepatitis B/C, EBV
Medications	NSAIDs MTX, TNF- $\alpha$ inhibitors Cimetidine Fluoxetine Potassium iodide
Malignancy	Leukemia/lymphoma Gammopathies (IgM, IgG)
Other	Serum sickness

**Table 3-43.** Systemic Involvement in Urticarial Vasculitis

<b>System</b>	<b>Associated Symptoms or Disease</b>
Musculoskeletal (50%)	Athralgias, myalgias
GI (15%–30%)	Recurrent abdominal pain, diarrhea, N/V
Pulmonary (20%)	SOB, severe COPD, laryngeal edema
Renal (20%–30%)	Glomerulonephritis or interstitial nephritis
Ocular (10%)	Uveitis, conjunctivitis, episcleritis
Constitutional symptoms	Fever, malaise, athralgias, myalgias

**Treatment (Table 3-44)****Key testing facts**

- **Schnitzler's syndrome:** urticarial vasculitis + IgM gammopathy + two of the following: fever, arthralgia, bone pain, ↑ESR, or ↑WBC

**Erythema elevatum diutinum****Epidemiology**

- Rare and chronic condition of middle-aged and older patients
- **HIV association**

**Pathophysiology**

- Immune complex deposition with repeat inflammation and partial healing → perivascular fibrosis
- May be a/w multiple systemic diseases (Table 3-45)

**Clinical presentation**

- Early lesions: **red-brown violaceous papulonodules** and plaques on **extensor** surfaces and near joints
- Later lesions: **firm nodules** and masses at previously inflamed sites
- Systemic associations: ocular (scleritis/uveitis) and athralgias

**Pathology**

- Early: LCV with interstitial neutrophils resembling neutrophilic dermatoses
- Late: perivascular storiform **fibrosis** (“**onion skin fibrosis**” around dermal vessels) with neutrophils

**Treatment**

- **Dapsone is the ToC**
- Other treatments: NSAIDs, TCN, and colchicine

**Table 3-44.** Treatment Approach for Urticarial Vasculitis

Primary	Antihistamines Oral steroids <b>Indomethacin</b>
Alternatives	<b>Dapsone</b> <b>Colchicine</b> Hydroxychloroquine
Severe	Prednisone+ MMF Rituximab IVIg

**Table 3-45.** Triggers of EED

Infection	$\beta$ -hemolytic Streptococci <b>HIV</b> HBV TB Syphilis
Autoimmune disease	IBD, celiac disease, SLE, RA
Hematologic malignancy	<b>IgA paraproteinemia/monoclonal gammopathy</b> Myelodysplasia



## Mixed cryoglobulinemia (see Cryoglobulinemia section)

### Granuloma faciale

#### Epidemiology

- Adults (Caucasian > African American) and M > F

#### Clinical features

- Single or multiple discrete **red-brown papules, plaques**, and nodules on the **face**, especially the nose, malar prominence, forehead, and ear
  - Some consider granuloma faciale and EED to be the same entity with different anatomic predilections
- May have **follicular prominence**, telangiectasias, or a “**peau d’orange**” appearance

#### Pathology

- LCV (findings may be difficult to identify)
- Grenz zone**
- Dense **mixed dermal infiltrate** consisting of **eosinophils, neutrophils**, lymphocytes and plasma cells (Fig. 3-84)

#### Treatment

- Intralesional triamcinolone** (2.5–5 mg/mL)
- Cryotherapy + intralesional triamcinolone
- Topical steroids
- Topical tacrolimus
- If unresponsive, consider dapsone (50–100 mg/day), colchicine, or plaquenil
- PDL

## Small to medium vessel vasculitis

- General features:
  - Mixture of signs of CSVV and medium vessel disease
    - Livedo, retiform purpura, ulcers, and subcutaneous nodules
    - Consider especially if there is pulmonary and/or renal involvement
- Types:
  - ANCA (+)**: Wegener’s granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome
  - Connective tissue disease (SLE and RA)
  - Mixed cryoglobulinemia (type II and III)

## ANCA positive vasculitis (Table 3-46) and (Table 3-47)

- General pathophysiology:
  - ANCA-mediated vascular injury is caused by neutrophils and monocytes that produce toxic oxygen metabolites
- Important ANCA associations** (boards tip: if you cannot remember the specific ANCA associations during the exam, just guess p-ANCA because it is the less specific autoantibody and is therefore associated w/ most of the diseases):
  - Granulomatosis with polyangiitis (Wegener’s): **c-ANCA**
  - Levamisole-induced vasculitis: **p-ANCA**
  - Churg-Strauss syndrome: **p-ANCA** >> c-ANCA
  - Microscopic polyangiitis: **p-ANCA** > c-ANCA
  - Minocycline-induced lupus erythematosus: **p-ANCA**

## Wegener’s granulomatosis (WG)

#### Epidemiology

- Middle aged adults + children

#### Pathophysiology

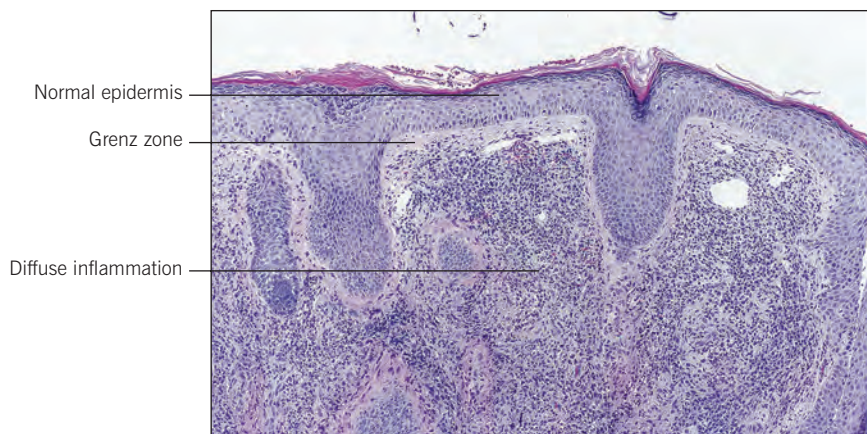
- c-ANCA mediated (anti-PR3)** Th1 immune response → granuloma formation
- Unknown triggers

#### Clinical presentation

- Triad of:
  - Necrotizing granulomas** of the upper and lower respiratory tract
    - Respiratory: cough, hemoptysis, and SOB
    - Nasal/sinus inflammation**: rhinorrhea, sinusitis, and purulent or bloody nasal discharge

**Table 3-46.** Features of ANCA Autoantibodies

<b>p-ANCA (less specific)</b>	Myeloperoxidase	Perinuclear staining	<b>CSS, MPA</b> > PAN Other autoimmune disease Chronic infection
<b>c-ANCA (highly specific)</b>	Serine Protease 3	Granular cytoplasmic staining	<b>Wegener’s</b> >> MPA



**Figure 3-84.** Granuloma faciale (low magnification). (From Rapini R. Practical Dermatopathology, 2nd Ed. Elsevier. 2012)

**Table 3-47.** ANCA(+) Vasculitides

Disorder	ANCA Type	Systemic Findings and Symptoms	Cutaneous Findings	Other Defining Features
Wegener's	c-ANCA	<b>Nasal/sinus:</b> sinusitis rhinorrhea <b>Pulmonary:</b> Cough Hemoptysis <b>Renal:</b> Glomerulonephritis with hematuria <b>CNS:</b> peripheral neuropathy, CVA	Palpable purpura <b>PG-like nodules</b> <b>Strawberry gums</b>	Granulomatous
Microscopic polyangiitis	p-ANCA > c-ANCA	<b>Nasal/sinus:</b> None <b>Pulmonary:</b> Alveolar hemorrhage <b>Renal:</b> Glomerulonephritis with hematuria <b>CNS:</b> Neuropathy, mononeuritis multiplex	Palpable purpura Livedo reticularis Retiform purpura Ulcers	<b>Non-granulomatous</b>
Churg-Strauss	p-ANCA	<b>Nasal/sinus:</b> Nasal polyps Allergic rhinitis <b>Pulmonary:</b> Asthma (adult-onset) <b>Renal:</b> less common <b>CNS:</b> mononeuritis multiplex, symmetric polyneuropathy <b>Cardiac:</b> cardiomyopathy, pericarditis, valvular disease <b>GI:</b> N/V, abdominal pain	Palpable purpura Painful subcutaneous nodules	Granulomatous eosinophilia

**Figure 3-85.** Wegener granulomatosis; strawberry gingiva. (From Andrews et al. *Andrews' Diseases of the Skin*, 11th Ed. Elsevier. 2011)

- **Systemic vasculitis**
  - Musculoskeletal: arthralgias
  - Ocular: conjunctivitis, proptosis, and keratitis
  - CNS: peripheral neuropathy and CVA
- **Glomerulonephritis**
  - Death from renal disease if left untreated (>80% 1 year mortality)
- Cutaneous findings: 10%–21% at initial presentation, 15%–46% throughout course of the disease
  - Palpable purpura in dependent areas
  - Oral ulcers are common – gingival hyperplasia with “strawberry gums” (Fig. 3-85) is rare, but pathognomonic

- Painful pyoderma gangrenosum-like nodules or necrotic ulcers
- Cutaneous disease a/w earlier onset and more widespread vasculitis
- Limited form: cutaneous or pulmonary subtype
- Constitutional symptoms: fever, weight loss, anorexia, and malaise

**Pathology**

- LCV + extravascular necrotizing palisading granulomas with basophilic debris (“blue granulomas”)

**Laboratory testing**

- ↑ESR and ↑WBC
- (+) c-ANCA
  - Sensitivity (up to 90%) and specificity (80%–100%)
  - May be absent in patients with localized WG
  - May have a role in disease monitoring
- Abnormal UA: microscopic hematuria or RBC casts
- Abnormal CXR: nodules, infiltrates, and cavities often found
- Sinus involvement: abnormal sinus X-ray, CT sinus, or nasal biopsy

**Treatment**

- Induction: cyclophosphamide (2 mg/kg per day) + oral steroids (Prednisone 1 mg/kg per day)
- Maintenance:
  - MTX (20–25 mg/week) +/- oral steroids
  - Azathioprine (2 mg/kg a day) + oral steroids
- Prognosis:
  - Relapse rate: 50% within 5 years

## Microscopic polyangiitis (MPA)

### Epidemiology

- M > F; peaks at 65–75 yo

### Pathophysiology

- Unclear, may be ANCA-mediated
- a/w infective endocarditis, meds, and malignancy

### Clinical presentation

- Cutaneous palpable purpura, petechiae > livedo reticularis, retiform purpura, ulcers, and splinter hemorrhages
- Constitutional symptoms may be present for months to years
- Systemic symptoms (Table 3-48):
  - Most common cause of **pulmonary-renal syndrome** (Table 3-49)

### Pathology

- LCV with segmental small > medium vessel vasculitis
- No **granuloma formation**, unlike WG or CSS

### Laboratory testing: see CSVV, especially:

- p-ANCA (anti-MPO, 60%) > c-ANCA (anti-PR3, 30%)
- Abnormal UA (proteinuria or hematuria)
- Abnormal CXR or CT (chest)
- Other: abnormal EMG or lung/nerve/kidney biopsy

### Treatment

- Induction:
  - Cyclophosphamide (2 mg/kg per day) + oral steroids (1 mg/kg per day)
  - Rituximab + cyclophosphamide
- Remission:
  - MTX or azathioprine, similar to WG
- Localized
  - TMP-SMX + oral steroids

## Churg-Strauss syndrome

### Epidemiology

- Peaks in middle age

**Table 3-48.** Comparison of MPA and PAN

	PAN	MPA
Renal: glomerulonephritis	–	+
HTN and microaneurysms	+	–
Pulmonary symptoms	–	+
ANCA(+)	– (less likely)	+ (more likely)
Hepatitis B or C association	+	–

**Table 3-49.** Systemic Involvement in Microscopic Polyangiitis

	Focal segmental necrotizing glomerulonephritis
Renal (79%–90%)	
Pulmonary (25%–50%)	Pulmonary capillaritis, pulmonary hemorrhage
Neurological (up to 33%)	Mononeuritis multiplex, peripheral neuropathy

### Pathophysiology:

- Mixed inflammatory and ANCA-mediated tissue damage with granuloma formation and neutrophilic vasculitis
- Possible triggers: rapid steroid taper, vaccination, leukotriene inhibitors, and anti-IgE Ab (omalizumab)

### Clinical presentation: three classic stages (Table 3-50)

- Cutaneous: presenting sign in 14%, but vast majority will develop at some point in disease course:
  - Palpable purpura on the lower extremities
  - Painful symmetric subcutaneous nodules of the extremities and scalp
- Systemic findings: Table 3-50

### Pathology

- LCV w/ mixed infiltrate of **eosinophils**, neutrophils, lymphocytes, and macrophages
- Palisading neutrophilic and **eosinophilic extravascular granulomas** with degenerated collagen fibers (“red granulomas”)

### Laboratory testing:

- (+)ANCA: patients more likely to have neurologic and renal disease
- (–)ANCA linked to cardiac disease
- **p-ANCA** > c-ANCA in leukotriene-associated Churg-Strauss
- **Eosinophilia** (eosinophils >1500  $\mu$ L)
- Leukocytosis
- $\uparrow$ IgE
- CXR: patchy infiltrates, interstitial disease, and nodular masses

### Treatment

- Oral steroids (1 mg/kg a day)
- Internal organ involvement:
  - Cyclophosphamide (2 mg/kg a day) + oral steroids

### Key testing facts

- **Asthma and eosinophilia** are key features
- **Limited renal involvement** unlike WG and MPA

**Table 3-50.** Stages of Churg-Strauss Syndrome

Stage	Presentation
1	<b>Adult-onset asthma</b> <b>Nasal polyps</b> <b>Allergic rhinitis</b>
2	Eosinophilia Pneumonia GI: N/V, abdominal pain
3	Systemic necrotizing vasculitis Pulmonary: asthma, sinusitis, allergic rhinitis Neurologic: mononeuritis multiplex, symmetric polyneuropathy Cardiac: pericarditis, valvular disease, endocardomyopathy (leading cause of death)

## Medium vessel vasculitis

### Subtypes: PAN and Kawasaki's disease

#### Polyarteritis nodosa (PAN)

##### Epidemiology

- M > F; peaks 40–60 yo
- Cutaneous form can occur at any age

##### Pathophysiology

- Possible triggers: meds, infections, inflammatory disease (IBD, SLE), and **hairy cell leukemia**; may be immune complex-mediated
- **a/w hepatitis B** (5%–7%) and hepatitis C
- Cutaneous form:
  - a/w streptococcal infection in children
  - Has been a/w minocycline

##### Clinical presentation

- Two forms:
  - Classic subtype with multi-system vasculitis
  - Cutaneous (Fig. 3-86) subtype with limited systemic involvement (Table 3-51)

##### Pathology:

- LCV
- Necrotizing arteritis of medium-sized arteries
  - In skin, these vessels are located in subcutis and at the dermopannicular junction
- **Microaneurysms** → thrombosis, ischemia, and necrosis
  - Microaneurysms seen on angiography of medium-sized vessels (coronary, renal, celiac, and mesenteric arteries)

- Later course defined by fibrosis
- DIF: IgM and/or C3 in the walls of cutaneous blood vessels

##### Laboratory testing: see CSVV

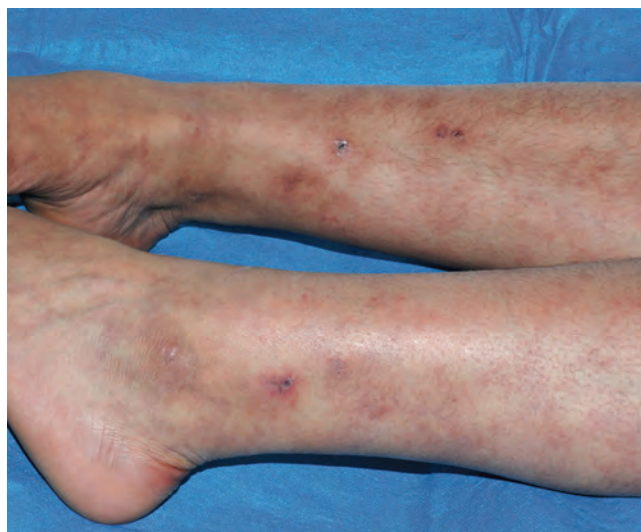
- CBC: anemia and leukocytosis
- UA for hematuria and RBC casts
- Hepatitis B and C
- ANCA (p-ANCA <20% positive)
- **Consider angiography if suspect microaneurysm or stenosis**
- In children, consider anti-streptolysin O

##### Treatment

- Cutaneous subtype:
  - Intralesional steroids, NSAIDs, and oral steroids for 3 to 6 months if severe skin involvement
  - Children: consider penicillin, given the association with streptococcal infection
- Severe systemic disease:
  - Cyclophosphamide (2 mg/kg a day) + oral steroids for 12 months
  - MTX (7.5–20 mg/week)
  - IVIG
- Hepatitis B (+):
  - Interferon-α +/- vidarabine/lamivudine + plasma exchange

##### Key testing facts

- Rare pulmonary involvement, unlike ANCA-associated vasculitides



**Figure 3-86.** Livedo reticularis of the abdomen and lower extremities with multiple small “punched out” ulcers in an adolescent with cutaneous PAN. This entity can overlap with the PAN-like syndrome with anti-phosphatidylserine-prothrombin complex antibodies that respond to anticoagulation. Courtesy, Julie V Schaffer, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 3-51.** Features of Classic and Cutaneous PAN

	Key Cutaneous Features	Systemic Features
Classic subtype (PAN)	Palpable purpura on lower extremities Painful single/multiple <b>subcutaneous nodule(s)</b> on lower extremities that may ulcerate Nodules may follow course of superficial blood vessels, especially in the lower extremities <b>Livedo reticularis</b> Rare digital or penile infarction	Constitutional symptoms: fever, weight loss, arthralgias, malaise Multi-organ involvement: Renal: <b>HTN and renal failure</b> (most common cause of death) Cardiac: cardiomyopathy, MI, arrhythmias Nervous system: paresthesias, motor or polyneuropathies (foot drop) GI: N/V, bowel infarction, hemorrhage, mesenteric ischemia GU: orchitis Multi-organ infarcts from aneurysms
Cutaneous subtype (C-PAN)	Pink to purple-red nodules on LE near the malleoli and may extend proximally Atrophie blanche: atrophic, ivory, stellate scars Livedo reticularis Digital gangrene	Constitutional symptoms: fever, myalgias Minimal organ involvement: Nervous: peripheral neuropathy Musculoskeletal: arthralgias, myalgias



## Kawasaki disease (acute febrile mucocutaneous lymph node syndrome)

### Epidemiology

- 80% of cases in kids <5 yo; M > F
- ↑incidence in Japanese

### Pathophysiology

- Unclear etiology, but likely due to infection by unknown agent
- Genetic and ethnic factors → ↑susceptibility
- Inflammation, scarring, stenosis, and aneurysm formation in the small, medium, and large musculoelastic arteries including the **coronary artery**

### Clinical presentation (Fig. 3-87)

- Fever for **at least 5 days** followed by:
  - **Conjunctival injection** (usually non-exudative)
  - Mucous membrane: lip/oral mucosa erythema, **fissured lips**, **strawberry tongue**, and injected oral and pharyngeal mucosa
  - **Cutaneous**: polymorphous eruption including psoriasiform, morbilliform, scarlatiniform (particularly **perineal with desquamation**), and EM-like lesions on hands/feet
  - **Cervical lymphadenopathy**
  - Extremity changes: **peripheral edema/erythema of hands/feet**, or periungual desquamation
- For diagnosis, need fever ≥5 days + four out of five of the above
- May get orange-brown or white transverse nail discoloration



**Figure 3-87.** Lip erythema, fissuring, and bleeding in a patient with Kawasaki disease. Oropharyngeal findings occur in 80% to 90% of patients, including redness of the lips, tongue, and throat. Lip fissuring and dryness are also common. (From Bayers S, et al. J Amer Acad Dermatol 69(4);501e1–501e11. Elsevier. 2013)

- Systemic complications:
  - Cardiac: **coronary artery aneurysms/ectasia** (secondary to vasculitis) and myocarditis
  - Musculoskeletal: arthritis/artralgias
  - Pulmonary: pneumonitis
  - CNS: aseptic meningitis and facial nerve palsies
  - Ophtho: anterior uveitis
  - GI: gastroenteritis, hepatomegaly, bile duct inflammation/hepatitis, jaundice, and pancreatitis

### Laboratory testing:

- CRP↑ and ESR↑
- CBC (**anemia**, **leukocytosis**, ↑neutrophil/eosinophils, and thrombocytosis)
- ↓albumin, sodium, potassium, and HDL
- LFTs↑, GGT↑
- Check **echocardiogram** at diagnosis, 2, 6, and 8 weeks

### Treatment

- **High-dose Aspirin** (80–100 mg/kg a day) + **IVIG** (2 g/kg)
  - If given within first 10 days → ↓coronary artery issues
- Resistant cases: IVIG + steroids, cyclophosphamide, cyclosporine/CIs, plasma exchange, TNF-α inhibitors, MTX, rituximab, and anakinra
- Maintenance: aspirin

### Key testing facts

- a/w myocardial infarction (**#1 cause of acquired pediatric heart disease in the US**)
- Patients <12 months do not respond as well to treatment

## Large vessel vasculitis

### Subtypes: temporal arteritis and Takayasu's arteritis

#### Temporal arteritis (giant cell arteritis)

##### Epidemiology

- More common in Caucasians, females
- >50 yo

##### Pathophysiology

- Vessel involved: any medium to large vessel (especially temporal artery)
- **Granulomatous vasculitis** → ischemia, occlusion, infarction, and aneurysm

##### Clinical presentation

- **Early**: **tenderness and erythema along scalp and temples** with possible cord-like nodule along temporal scalp
  - Other cutaneous symptoms: erythema, purpura, alopecia of overlying skin, and scalp necrosis
- **Unilateral temporal headache**
- **Loss of temporal pulse**
- **Jaw claudication**
- Glossitis, necrosis of anterior tongue (lingual artery)

**Table 3-52.** Summary of Organ System Involvement in Vasculitides

Organ System	PAN	WG	MPA	CSS	CV	UV	HSP
Cutaneous	40%–50%				90%–100%		
Pulmonary	rare*	90%	35%	60%			
Renal	30%	80%–90%		35%			50%
ENT		90%		50%			
Musculoskeletal	40%–75%						
Neurologic	50%–60%		35%	70%			
Gastrointestinal	30%	40%–50%			30%		60%

\*Classic PAN spares the lungs

- **Late:** ulceration or gangrene
- **Systemic findings:**
  - **Polymyalgia rheumatica** (40%–60%) with limb and girdle muscle pain, stiffness, and weakness
  - Fever and weight loss
  - Neurologic: **vision loss** (14%), stroke, subarachnoid hemorrhage, and altered mental status

### Pathology

- Segmental **granulomatous large vessel arteritis** with giant cells
- Disruption of media with fragmentation of the internal elastic lamina

### Laboratory workup

- ↑ESR and ↑CRP
- Anticardiolipin antibody (may be ↑)
- MRA
- Temporal artery biopsy

### Treatment

- Aspirin 81 mg/day + oral steroids (40–60 mg/day)
- Consider methylprednisolone (1 g/day for 3–5 days) if acute visual loss

## Takayasu's arteritis

### Epidemiology

- F > M; <40 yo

### Pathophysiology

- Vessel involved: **aorta** and its main branches
- Granulomatous vasculitis → stenosis, occlusion, and aneurysms

### Clinical presentation

- Cutaneous symptoms seen in 50% of individuals, including:
  - Purpura
  - Erythematous subcutaneous nodules, EN-like lesions, PG-like lesions
  - Raynaud's phenomenon and digital gangrene
- Systemic symptoms:
  - Constitutional symptoms: fever, fatigue, malaise, night sweats, and weight loss
  - HTN
  - Loss of carotid or radial pulse

**Table 3-53.** Comparison of Cryoglobulinemias

Type	Cause	Associations
Type 1 (20%–25%)	<b>Monoclonal</b> immunoglobulin ( <b>IgM</b> >> IgG, IgA, light chains)	<b>Lymphoproliferative disorders</b> CLL Multiple myeloma Waldenstrom's macroglobulinemia B-cell non-Hodgkin's lymphoma
<i>Mixed Cryoglobulinemias</i>		
Types 2 and 3 (75%–80%)	<b>Monoclonal (Type 2) or polyclonal (Type 3) IgM</b> complexes with <b>polyclonal IgG</b>	Infections <b>Hepatitis C</b> (cutaneous symptoms more common) Autoimmune disease SLE (nephritis risk with cryoglobulins) Sjogren's RA

### Pathology

- Granulomatous inflammation of the aorta and its major branches

### Laboratory workup

- ↑ESR
- MRA with visualization of all branches of the aortic arch

### Treatment

- Oral prednisone (1 mg/kg) for 1 to 3 months with a 6 to 12 month taper
- MTX 15–25 mg/week + prednisone
- Cyclophosphamide
- Trials with infliximab or etanercept are promising
- Surgical intervention for cerebral hypoperfusion, valvular insufficiency, and aneurysms
- Summary of organ system involvement in various vasculitides ([Table 3-52](#))

## Cryoglobulinemias

### Epidemiology:

- Varies geographically – likely **related to HCV** prevalence
- F > M; average age = 50 yo

### Pathophysiology:

- Cryoglobulins are immunoglobulins that precipitate at colder temperatures; various triggers ([Table 3-53](#))

- **Type I: ↑monoclonal cryoglobulins (IgM >> IgG, IgA, light chains)** → complete occlusion of vessel lumens w/ **hyaline material**
  - **Lacks LCV**
- **Type II and III (mixed type):** complexed immunoglobulins will precipitate at cooler temperature and occlude vessels → triggers complement → LCV

#### Clinical presentation

- Cutaneous findings:
  - Type I findings:
    - Raynaud's phenomenon
    - Purpura, **livedo reticularis**, and ulceration
    - Cold-induced **acrocyanosis** of helices
  - Type II and III findings:
    - **Palpable purpura** and urticarial lesions
    - Systemic findings common

#### Pathology

- Type I: **occlusive vasculopathy** with vessels completely filled by **homogenous hyaline material**; **lacks LCV**
- Types II and III: characteristic features of LCV

#### Laboratory testing

- ↑cryoglobulins
- Complement (**hypocomplementemia in 90%**; C4↓)
- RF(+) (Types 2 and 3)
- Hepatitis B/C
- LFTs

#### Treatment: treat underlying disease

- HCV-related:
  - **Interferon-α +/- ribavirin** to prevent relapse
  - Low dose oral steroids (0.1–0.3 mg/kg per day if arthralgia/weakness present)
  - High dose (0.5–1.5 mg/kg per day) for renal or nervous system involvement
- HCV-unrelated disease (connective tissue or malignancy related) is less clear

### Thrombosis and thrombotic syndromes

- Consider occlusive vasculopathy if **livedo reticularis** and/or **retiform purpura** is present (signs of vascular occlusion)
- Two broad categories of thrombotic syndromes:
  - **Acutely sick patient:** DIC, purpura fulminans, TTP, Coumadin necrosis, heparin-induced skin necrosis, TTP, PNH, HUS, cholesterol emboli, and septic vasculitis
  - **Purpura fulminans:** acute syndrome of progressive hemorrhagic skin necrosis and disseminated intravascular coagulation (DIC); children > adults; may be idiopathic, triggered by an infection (most commonly meningococcal, **streptococcal**, staphylococcal, or varicella), or due to congenital deficiency in protein C or S; sudden onset of tender purpura and ecchymosis that often expand rapidly with a rim of erythema and central hemorrhagic

bulla and/or necrosis; favor acral distribution and buttocks

- **Non-sick patient:** APLS, livedoid vasculopathy, inherited coagulopathies (protein C, S, anti-thrombin III, Factor V Leiden), and type I cryoglobulinemia

### Important subtypes

#### Anti-phospholipid syndrome (APLS)

##### Epidemiology

- Mainly young women

##### Pathophysiology

- Unclear etiology
- a/w immunoglobulins that are reactive with phospholipids
- Predisposition to thrombosis

##### Clinical presentation

- History of vascular thrombosis, **premature birth**, **miscarriage**, and labile blood pressure
- Cutaneous features:
  - Livedo reticularis (most common finding)
  - Leg ulcers, pseudovasculitis, digital gangrene, cutaneous necrosis, splinter hemorrhages, and **retiform purpura (suggestive of occlusion)**
  - Atrophie blanche
- Systemic features:
  - DVT, PE, stroke, renal infarct, myocardial infarction, arthritis, and epilepsy
  - **a/w SLE (most common)** and other autoimmune conditions including RA and ulcerative colitis
- Precipitants: surgery, meds (HCTZ, OCPs, ACEI), and infection

##### Pathology:

- Occlusion of arteries and arterioles w/ **fibrin thrombi**; minimal inflammation; **lacks LCV**

##### Laboratory findings:

- (+)antiphospholipid antibodies: **anti-cardiolipin antibodies (most sensitive, most commonly positive)**, **lupus anticoagulant**, and **anti-β<sub>2</sub>-glycoprotein I antibody (most specific)** – one or multiple may be positive
- **False-(+) syphilis serology**

##### Treatment

- Empiric anticoagulation, anti-platelet agents, and antimalarial agents in those with concurrent lupus

#### Livedoid vasculopathy (atrophie blanche)

##### Epidemiology:

- F > M; mean age of onset = 45 yo
- Worse in summer

##### Pathogenesis:

- Unknown, but linked to coagulation disorder

*Clinical presentation:*

- Burning pain along the ankle prior to ulceration
- Cutaneous findings:
  - Purpuric lesions progress to **painful and irregular leg ulcers**
  - Livedo reticularis
  - **Atrophie blanche**: porcelain-white scar (Fig. 3-88)
  - Post-inflammatory hyperpigmentation
- Systemic findings
  - a/w autoimmune conditions
    - SLE, scleroderma, and APLS
  - a/w **hypercoagulable disorders**
    - Hyperhomocysteinemia, Factor V Leiden, prothrombin mutations, protein C deficiency
  - a/w atherosclerosis and stasis

*Pathology*

- Segmental **hyalinization and thrombosis of small vessels** in the upper and mid dermis
- Late stage with epidermal atrophy and **hyalinized vessels**

*Laboratory findings*

- Perform **coagulopathy workup** (cryoglobulins, homocysteine, protein C/S, anti-thrombin III, ANA, anti-cardiolipin Ab, Factor V mutation, and prothrombin mutation)

*Treatment*

- **Aspirin**
- Dipyridamole
- **Pentoxifylline**
- In recurrent or recalcitrant cases:
  - Anticoagulation (heparin, warfarin, and rivaroxaban)
  - Oral steroids
  - Sildenafil reported in limited cases



**Figure 3-88.** Atrophie blanche from livedoid vasculopathy. (From Thornsberry LA, et al. J Amer Acad Dermatol 69(3):450–462. Elsevier. 2013.)

**Other vasculopathies (Table 3-54)****Other vascular disorders****Venous lake**

- Small (<1 cm) dark blue soft papules on **lips** primarily
- Large ectatic vessel seen in dermis

**Telangiectasia**

- Permanently dilated dermal vessels that appear red
  - Primary:
    - Spider telangiectasia (can also occur secondary to ↑ **estrogen**)
    - Hereditary benign telangiectasia
    - Angioma serpiginosum
      - ◆ Females <20 yo
      - ◆ Pinpoint punctate blanching red-purple petechiae in clusters/patches in serpiginous pattern typically on one **extremity**
    - Unilateral nevoid telangiectasia
      - ◆ Telangiectasias in trigeminal/upper cervical dermatomes +/- Blaschko's lines
      - ◆ Some cases are acquired, secondary to ↑estrogen
    - Generalized essential telangiectasia
      - ◆ Typically **adult women**
      - ◆ **Starts on lower extremities and spreads**, involving large areas
    - Cutaneous collagenous vasculopathy
      - ◆ Large anatomic areas – does not have female predominance or centripetal spread
      - ◆ Ectatic dermal vessels with **thick hyalinized BMZ surrounding vessels (stain (+) with collagen IV/PAS-positive)**
      - ◆ Not responsive to laser
  - Secondary:
    - Photodamage, post-radiation, telangiectatic rosacea, involuted hemangioma, estrogen-related (e.g., **liver disease, pregnancy**, hormone replacement therapy, or OCPs), corticosteroid use, AICTDs (e.g., **CREST syndrome**), HIV infection (chest), mastocytosis (TMPE), carcinoid, and drugs (**CCBs** → telangiectasias in sun-exposed areas)
    - **Genodermatoses**: CMTC, HHT, A-T, K-T syndrome, Rombo, Bloom, Rothmund-Thomson, dyskeratosis congenita, XP, Goltz (within Blaschko's lines), prolidase deficiency, and hypotrichosis-lymphedema-telangiectasia syndrome

**Erythromelalgia**

- **Red, painful/burning, edematous, hot distal extremities** (especially **lower extremities** – feet/lower legs)
- Episodes usually late day/night
- Many cases a/w **small fiber neuropathy**
- Worse with heat/activity; relieved with cooling, classically “**plunging feet into ice cold water**”
- Type 1: occurs with **thrombocythemia**
  - May → ischemic necrosis
  - Histologically see occlusive thrombi
  - Aspirin and hydroxyurea may be helpful



**Table 3-54.** Vascular Disorders Not Otherwise Discussed

Cause	Key Features	Laboratory Testing and Treatment
<b>Emboli: cholesterol, bacterial or fungal endocarditis, oxalate</b>		
Cholesterol emboli	<p><b>p/w livedo reticularis</b> &gt; retiform purpura or gangrene of the distal extremities and digits. Clinical setting: <b>post-catheterization (hrs–days), thrombolytics (hrs–days), anticoagulation (1–2 mos)</b>; may be febrile, hypertensive, and/or with altered mental status</p> <p>Pathogenesis: fragmentation of an atherosclerotic plaque that embolizes</p> <p>Histology: <b>cholesterol clefts in small vessels</b></p>	<p><u>Laboratory findings:</u></p> <p><b>Eosinophilia</b> common</p> <p>↑ESR</p> <p>↑BUN/Cr</p> <p><u>Treatment:</u></p> <p>supportive, aspirin, anti-platelet, statins</p>
<b>Inflammation: pigmented purpura, hypergammaglobulinemic purpura of Waldenström</b>		
Pigmented purpura (capillaritis)	<p>Group of disorders with clustered petechial hemorrhage</p> <p>Pathophysiology: inflammation of the capillaries with resultant hemorrhage</p> <p><b>Types:</b></p> <p><b>Schamberg's:</b> cayenne-pepper purpura on the lower extremities (esp. shin, ankles) that can extend; middle-aged to older adults</p> <p><b>Purpura annularis telangiectodes of Majocchi:</b> annular patches with punctate petechiae on trunk and lower extremity in adolescent/young-adult women</p> <p><b>Lichenoid dermatitis of Guogeroth and Blum:</b> rust-colored lichenoid papules and Schamberg-like purpuric lesions in middle-aged to older men</p> <p><b>Eczematid-like purpura of Doucas and Kapetanakis:</b> scaly and eczematous petechiae and purpura in middle-aged to older men</p> <p><b>Lichen aureus:</b> solitary golden or rust-colored patch on the lower extremities</p> <p><b>Linear pigmented purpura:</b> unilateral, linear eruption of yellow-brown macules, patches, and red-brown purpura; adolescents and children mainly</p> <p>Histology: hemosiderin containing macrophages with RBC extravasation, endothelial swelling, and a perivascular lymphocytic infiltrate. Guogeroth: lichenoid infiltrate; Doucas and Kapetanakis: spongiosis and parakeratosis</p>	<p>Treatment: topical steroids for pruritus, PUVA, NB-UVB, compression stockings</p>
Hypergammaglobulinemic purpura of Waldenström	<p>Crops of burning/stinging petechiae and/or purpura on the lower extremities, often seen in women. <b>a/w polyclonal gammopathy</b> (IgG and IgA RF), and CTD (Sjogren's)</p> <p>Pathophysiology: unknown cause, likely immune complex-mediated (IgG and IgA)</p> <p>Histology: hemorrhage, mild perivascular lymphocytic infiltrate, or LCV</p>	<p>Treatment: aspirin and compression stockings controversial; Avoid triggers, including alcohol</p>
<b>Hemorrhage: trauma, thrombocytopenia, platelet dysfunction, medication (aspirin, steroids)</b>		
<b>Other: levamisole-induced vasculitis, Degos disease, Sneddon syndrome, Schnitzler's syndrome</b>		
Levamisole-induced vasculitis	<p><b>Cocaine may contain levamisole</b>, an antihelminthic agent, which ↑ its stimulant effects and bulk</p> <p>It has recently been shown to cause <b>vasculitis/vasculopathy</b></p> <p>Presentation: purpura and necrosis of the <b>earlobes</b> (but also nose, cheek, extremities), LCV-like lesions, ecchymoses, and systemic vasculitis, especially of the kidney/lung/testes</p> <p>Histology: thrombotic vasculitis/LCV +/-vascular occlusion</p>	<p><u>Laboratory findings:</u></p> <p>↑ABs to <b>p-ANCA (&gt;80%)</b>, c-ANCA (50%), and human neutrophil elastase</p> <p>Agranulocytosis</p> <p>Leukopenia</p> <p><u>Treatment:</u></p> <p>Resolution once tainted cocaine stopped, occasionally immunosuppressants</p>
Degos disease (malignant atrophic papulosis)	<p>Crops of small <b>erythematous papules that develop a central depression/ivory scar</b>, peripheral erythema and surrounding telangiectasias (~atrophie blanche)</p> <p>Systemic symptoms include: <b>GI (bowel perforation)</b></p> <p>Seen in <b>young and middle-aged men</b></p> <p>Pathophysiology: unknown, possible vasculopathy</p> <p>Histology: wedge-shaped area w/ dermal edema, mucin, sclerosis; vascular thrombosis</p>	<p>Treatment:</p> <p>No proven treatment</p> <p>Aspirin +/- pentoxifylline</p>
Sneddon syndrome	<p><b>Livedo racemosa</b> and livedoid vasculopathy with labile blood pressure and <b>CNS disease (TIA, stroke, dementia)</b>, and extracerebral thrombosis. Seen in <b>young women</b> aged 20–30</p> <p>Pathophysiology: a/w <b>APLS</b>, vasculopathy or vasculocoagulopathy</p> <p>Histology: endothelial inflammation; subendothelial intimal smooth muscle proliferation; partial or complete occlusion of arterioles</p>	<p>↑anti-phospholipid antibodies</p> <p>Treatment:</p> <p>warfarin (INR 2-3)</p>

- Type 2: primary idiopathic
  - May occur in childhood and be familial (SCN9A mutations)
  - May treat with sodium channel blockers (e.g., mexiletine and flecainide)
- Type 3: occurs with underlying condition (NOT thrombocythemia)
- Treatment: supportive treatments, capsaicin cream, amitriptyline-ketamine gel, lidocaine patches or IV, antidepressants, anticonvulsants, CCBs, misoprostol,

nitroprusside, prostaglandin E1, and anesthetic epidural infusions/lumbar blocks and sympathectomies

### Livedo reticularis (LR)

- Reticulated vascular pattern that is usually benign (physiologic), but may be a/w an underlying disorder (e.g., AICTD or APLS)
  - **Physiologic:** secondary to vasospastic response to cold and improves with heat; processes that → ↓ blood

flow to and within skin or ↓ blood draining out of skin → deoxygenated blood in venous plexus → livedo appearance

- Physiologic type usually with fine complete network
- **Idiopathic/primary LR:** persistent arteriole vasospasm → persistent LR of lower extremities
- **LR secondary to vasospasm:** may be seen with AICTDs and Raynaud's
- **LR secondary to vessel wall issues:** usually medium vessel vasculitis (especially cutaneous PAN; also systemic PAN, cryoglobulinemic vasculitis, vasculitis secondary to AICTDs); can also be seen in calciphylaxis
  - **Livedo racemosa** = larger branching and incomplete rings (vs smaller complete rings of LR)
    - ◆ Seen in Sneddon syndrome and APLS
- **LR secondary to intraluminal issues: slow blood flow within vessels** (cryoglobulinemia, cryofibrinogenemia, PCV, thrombocytosis, APLS, and protein C/protein S/anti-thrombin III deficiencies) vs **obstruction of vessels** (cholesterol emboli, APLS, heparin/warfarin necrosis, hyperoxaluria, and livedoid vasculopathy)
- **Other LR causes:** amantadine use, pheochromocytoma, and reflex sympathetic dystrophy
- Biopsy technique: elliptical excisional biopsy from normal appearing skin in center of net pattern

### Auriculotemporal nerve syndrome (Frey syndrome)

- Most common **complication of parotidectomy**
  - Nerve damage may also be caused by parotitis, parotid abscess, cerebellopontine tumors, or surgery
- Due to aberrant regeneration of parasympathetic fibers of auriculotemporal nerve after injury
- Most common cause in **children** is nerve damage from **forceps delivery** (presents after starting solid foods)
- p/w unilateral (> bilateral) flushing and/or sweating in the distribution of the auriculotemporal nerve
- Usually **stimulated by ingestion of certain foods**, especially sour or spicy foods; less commonly triggered by olfactory or tactile stimuli
- Changes are typically transient; botulinum toxin has been employed

## 3.23 PANNICULITIDES AND LIPODYSTROPHIES

### Erythema nodosum (EN)

#### Epidemiology

- Most common panniculitis, especially women in second to fourth decades

#### Pathogenesis

- Delayed hypersensitivity response (Th1 cytokine pattern) to various antigens

- Idiopathic most common cause, followed by **streptococcal infections (#1 identifiable cause)**, other infections (bacterial GI infections (*Yersinia*, *Salmonella*, *Campylobacter*), viral URIs, coccidioidomycosis, tuberculosis, and histoplasmosis), drugs (estrogens/OCPs, sulfonamides, and NSAIDs), sarcoidosis, and IBD (Crohn's > UC)
  - **Lofgren's syndrome:** type of sarcoidosis w/ EN, hilar lymphadenopathy, fever, polyarthritides, and uveitis; a/w good prognosis

#### Clinical features

- Acute, **tender subcutaneous nodules** on **pretibial areas** (most commonly) bilaterally with overlying erythema to **bruise-like patches**
  - Develop over 1–2 weeks, then resolve spontaneously
  - New lesions may develop over 1–2 months
  - Can be a/w fever, arthralgias, malaise (may precede cutaneous findings)
- Chronic forms (**subacute nodular migratory panniculitis/erythema nodosum migrans**) can occur
  - Women mainly; unilateral; migrating centrifugally expanding nodules (less tender than EN)
  - Usually idiopathic, but may be a/w *Streptococcus* infection; treat with SSKI

#### Histopathology

- **Septal panniculitis** with **thickening/fibrosis of septae**
- **Neutrophils** seen particularly in early lesions
- **Miescher's migrogranulomas:** small histiocytic aggregates surrounding a central stellate cleft; located in SQ fat septa
- +/- thrombophlebitis (more common in EN-like lesions seen in Behcet's disease)

#### Treatment/clinical course

- Lesions last a few days to weeks, then **resolve w/o scarring**; recurrences may occur
- Treat underlying medical issue (if identified)
- Options for treatment of EN: bed rest/elevation, **NSAIDs**, **SSKI**, colchicine (especially for Behcet's-associated EN), dapsone, TNF- $\alpha$  inhibitors (**especially for IBD-associated EN**), and systemic immunosuppressants

#### Additional boards factoids

- EN a/w improved prognosis of coccidioidomycosis and sarcoidosis

### Alpha<sub>1</sub>-antitrypsin deficiency panniculitis

#### Pathogenesis

- alpha<sub>1</sub>-antitrypsin (serine protease inhibitor made in liver) deficiency → dysregulation of immune system and ↑neutrophils → release of proteolytic enzymes → fat necrosis
- Various alleles:
  - M = medium (normal quantities of enzyme)
  - S = slow (moderately ↓quantities of enzyme)
  - Z = very slow (severely ↓quantities of enzyme)
- Heterozygotes with one copy of Z or S have mild/moderate deficiency (PiMS, PiMZ); **most severe dz = homozygous for Z allele (PiZZ)**

### Clinical features

- Red/bruised tender plaques – lower trunk and proximal extremities → ulceration/necrosis → **oily discharge**
- Preceding trauma in one third
- Lesions quite resistant to treatment → permanent **scarring/atrophy**
- a/w **chronic liver dz (cirrhosis), emphysema, pancreatitis, membranoproliferative glomerulonephritis, c-ANCA vasculitis, and angioedema**

### Histopathology

- Lobular or mixed panniculitis w/ neutrophils
- **Liquefactive necrosis of SQ fat** (lobules and septa) and dermis

### Treatment

- ToC =  $\alpha_1$ -antitrypsin replacement → rapid improvement
- Other treatments: doxycycline, colchicine, cyclophosphamide, dapsone, ↓alcohol consumption, plasma exchange, and liver transplant

## Erythema induratum/nodular vasculitis

### Epidemiology

- Women primarily; 30–40 yo

### Pathogenesis

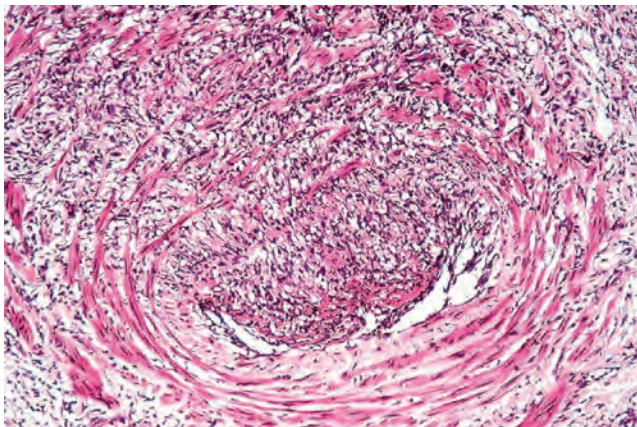
- May be a/w **tuberculosis (erythema induratum of Bazin)** or idiopathic (nodular vasculitis)
  - Tissue culture for mycobacteria usually negative → PCR tests for *M. tuberculosis* more sensitive
- Likely type IV cell-mediated response to antigen

### Clinical features

- Tender, recurrent red-purple nodules and plaques on **calves** most commonly
- May ulcerate, drain and scar

### Histopathology

- **Lobular and septal panniculitis** (Fig. 3-89) w/ neutrophils, lymphocytes, macrophages, giant cells +



**Figure 3-89.** Nodular vasculitis: vascular involvement as seen in this field is a characteristic feature. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)

**medium vessel vasculitis** (found in connective tissue septa/fat lobules)

- **Main DDx = PAN** (both affect medium-sized vessels, but **PAN does not have any significant involvement of the fat lobules themselves**)
- May have caseous or coagulative necrosis +/- palisading granulomas

### Treatment

- Treat TB if present; otherwise supportive care + various systemic treatments (corticosteroids, NSAIDs, TCNs, and SSKI)

## Pancreatic panniculitis

### Pathogenesis

- a/w pancreatic disorders (e.g., **pancreatitis, carcinoma, and pseudocysts**)
- Due to hydrolysis of fat by **lipase, amylase, and trypsin**
  - ↑serum levels of any (or all) of these three enzymes are detectable

### Clinical features

- **Subcutaneous nodules of legs** (most common site)
  - May occur prior to knowledge of pancreatic issues
  - Lesions are red/brown, firm, and tender → may ulcerate and release oily discharge
- May have concurrent systemic symptoms:
  - **Schmid's triad** (nodular lesions + polyarthrititis + eosinophilia) → a/w **poor prognosis**

### Histopathology

- Mixed panniculitis w/ "**ghost cell**" (anucleate necrotic adipocytes) formation and fat necrosis w/ **saponification** by calcium salts → basophilic color of damaged fat lobules

### Treatment

- Treat underlying pancreatic disorder

## Lipodermatosclerosis

### Epidemiology

- Middle aged/elderly
- F > M

### Pathogenesis

- Due to combination of **venous insufficiency** and **fibrinolytic abnormalities** → ↑capillary permeability → fibrinogen leakage → fibrin cuffs form around vessels → ↓O<sub>2</sub> exchange/tissue anoxia → cystic fat necrosis +/- dermal stasis changes

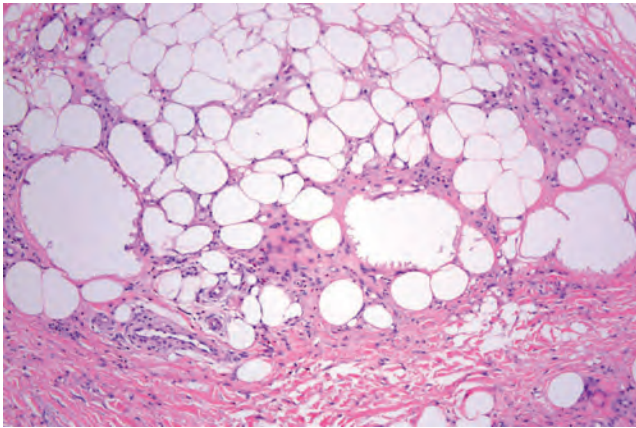
### Clinical features

- Acute (rubor, dolor, and calor) → chronic (well-defined induration, hyperpigmentation, "**inverted wine bottle**" appearance from sclerosis)
- **Medial lower leg**, superior to malleolus

### Histopathology

- **Septal thickening** (Fig. 3-90) and fibrosis, **cystic fat necrosis** w/ surrounding lipophages (histiocytes that





**Figure 3-90.** Sclerosing panniculitis: close up view of microcysts. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)

have engulfed lipid from necrotic lipocytes), mild non-specific inflammation, **lipomembranous change**, +/- signs of stasis changes (angioplasia, inflammation, and fibrosis)

#### Treatment

- Leg compression and elevation
- Systemic options: **danazol**, oxandrolone, and pentoxifylline

### Panniculitis secondary to external factors

- **Cold panniculitis**: acute, firm, painful, cool (in temperature), and erythematous plaques/nodules that develop 1–3 days post cold exposure; **most commonly affects areas of prominent fat distribution (central cheek, thighs, and back)**
  - Named variants:
    - **Popcicle panniculitis**: seen in **infants** mainly on **cheeks** (due to higher saturated: unsaturated fatty acid ratio)
    - **Equestrian panniculitis**: **young women equestrians** on thighs
  - In neonates risk factors include head or whole body hypothermia for hypoxic-ischemic encephalopathy and use of ice therapy for supraventricular tachycardia
  - Histology: **lobular panniculitis** + typical **pernio changes** (superficial and deep PV/peri-eccrine lymphohistiocytic infiltrate w/papillary dermal edema)
  - Resolves over several weeks; lipoatrophy may develop in affected areas
- **Physical trauma/foreign material**:
  - **Sclerosing lipogranuloma**: male genitalia (penis mainly) due to injection of oil-based materials for augmentation
  - Other injectable agents (e.g., factitial, cosmetic)
  - Blunt trauma
  - Histologic clues: vacuolated spaces, foreign material (e.g., “**Swiss cheese**” appearance in **sclerosing lipogranuloma**), and evidence of needle stick injury

### Lipodystrophies

- Disorders with selective loss of fat +/- fat accumulation in other areas (Table 3-55)

## 3.24 DERMATOSES OF PREGNANCY

### Physiologic changes during pregnancy

- Vary widely, but most testable are **linea nigra**, **melasma**, **telogen effluvium**, **striae gravidarum**, and **palmar erythema**

### Dermatoses of pregnancy (discussed in Table 3-56)

## 3.25 HAIR, NAIL, AND MUCOSAL DISORDERS

### Non-scarring alopecia

### Androgenetic alopecia (AGA)

#### Epidemiology

- 80% men and 50% women by age 70

#### Pathogenesis

- Strong genetic predisposition (polygenic)
- In men,  $\uparrow$ **dihydrotestosterone (DHT)** expression plays a role
  - **5 $\alpha$ -reductase** enzymes catalyze conversion of testosterone to DHT:
    - Type I 5  $\alpha$ -reductase – **skin, hair follicles, and sebaceous glands**
    - Type II 5  $\alpha$ -reductase – **prostate mainly, but also hair (inner root sheath)**
      - ◆ Absence prevents male AGA

#### Clinical features

- Norwood-Hamilton classification system in men
  - Progressive **frontotemporal hairline recession** and thinning over frontal crown and vertex scalp
- Ludwig scale in women
  - **Preservation of frontal hairline** with progressive **thinning from vertex** to frontal scalp
  - Increased central part width creates “**Christmas tree pattern**”

#### Histology

- $\uparrow$ **vellus hairs** and **miniaturized hairs** (both types are fine, short, non- or lightly-pigmented)
  - Vellus hairs: have always existed as small hairs (never were terminal hairs)
  - “Miniaturized hairs:” hairs that were previously large terminal hairs but have shrunk over time to become small hairs roughly the size of vellus hairs



**Table 3-55.** Lipodystrophies

Disorder	Pathogenesis	Clinical Features	Other Facts
Congenital generalized lipodystrophy (Berardinelli-Seip syndrome)	AR AGPAT2 (type 1), BSCL2/seipin (type 2), CAV1 (type 3) Highest frequency in Brazil	<b>Loss of fat in face</b> (e.g., preauricular), trunk, extremities, viscera +/- palmo-planar/retro-orbital/tongue/breasts/vulva/peri-articular ((-) in type 1 and 3, (+) in type 2) Acanthosis nigricans, hypertrichosis, xanthomas Muscular hypertrophy appearance Osteosclerotic and lytic skeletal changes Masculinization in women/ enlarged genitalia in kids only Starts at birth	Diabetes/insulin resistance more common, including metabolic syndrome ↑Triglycerides ↓HDL Vitamin D resistance in type 3 PCOS, infertility (women) <b>hypertrophic cardiomyopathy</b> (usually fatal – mean lifespan = 32 yo; ↑ in type 2), atherosclerosis, liver failure, fatty liver/cirrhosis, organomegaly, acute pancreatitis, proteinuric nephropathy, mental retardation (↑ in type 2)
Familial partial lipodystrophy (Köbberling-Dunnigan syndrome)	AD LMNA, PPARγ (milder clinical features but worse metabolic features), AKT2, PLIN1	<b>Loss of fat on extremities/buttocks</b> +/- trunk (anterior > posterior) <b>↑fat on face/neck</b> , labia majora <b>muscular hypertrophy appearance</b> w/ prominent veins Starts at puberty tuberous xanthomas, acanthosis nigricans, hirsutism	Diabetes/insulin resistance more common ↑Triglycerides ↓HDL (worse w/ PPARγ type) Acute pancreatitis, fatty liver/cirrhosis, menstrual issues, PCOS, atherosclerosis, HCM worse in women subtype with mandibuloacral dysplasia (LMNA or ZMPSTE24 mutation)
Acquired generalized lipodystrophy (Lawrence syndrome)	Unknown	Loss of fat on face, trunk, extremities ( <b>including palms/ soles</b> ) Loss of visceral fat but bone marrow fat preserved ( <b>unlike</b> congenital generalized lipodystrophy) Muscular appearance due to loss of fat Acanthosis nigricans, hyperpigmentation, eruptive xanthomas, hirsutism Starts in childhood/adolescence (7 yo in panniculitis variant, 15 yo in autoimmune variant, 20 yo in idiopathic variant)	Diabetes/insulin resistance more common ↑Triglycerides ↓HDL 30% have preceding AICTD (type 2 variant; e.g. juvenile DM) or infection, and ¼ have preceding <b>panniculitis</b> (type 1 variant) clitoromegaly, PCOS, menstrual issues Coronary artery dz, PVD Organomegaly Fatty liver/cirrhosis (can be fatal, more so than in congenital generalized lipodystrophy) Cirrhosis, proteinuric nephropathy
Acquired partial lipodystrophy (Barraquer-Simons syndrome)	Sporadic vs AD LMNB2 Linked to infections and autoimmune diseases	<b>F &gt;&gt; M</b> Loss of fat on face ( <b>cadaveric facies</b> ), upper extremities, trunk (spreads in <b>cephalocaudal</b> direction, sparing lower extremities) ↑fat in hips, legs, gluteal region acanthosis nigricans, hirsutism starts in childhood/adolescence	↑Triglycerides and DM2/ insulin resistance may occur but metabolic syndrome less common than other disorders may be preceded by infection and/or a/w AICTD (SLE, DM) Menstrual issues <b>Membranoproliferative glomerulonephritis</b> (several years after lipodystrophy, 1/5 pts) <b>↓C3 and ↑C3 nephritic factor</b> (polyclonal IgG; binds C3) → activates alternative complement pathway → adipocyte death and ↑ <i>N. meningitidis</i> infections

- ↓terminal hairs (thick, long, and deeply-pigmented)
  - Due to progressive miniaturization process
- Anisotrichosis: ↑variability in hair shaft size
  - Due to progressive process of terminal hairs becoming “miniaturized” to resemble native vellus hairs
  - This finding is a very helpful clue on horizontal sections
- Shortened anagen phase → slightly ↑ telogen:anagen ratio (“catagen/telogen shift”)
  - Degree of catagen/telogen shift is mild in androgenetic → not nearly as dramatic of a catagen/telogen shift as in alopecia areata or trichotillomania/traction alopecia
- ↑fibrous streamers: fibromucinous tract remnants underneath miniaturized or telogen hairs
  - ↑streamers are a helpful clue that suggests one of two processes:
    - Hairs are undergoing **miniaturization process** (transforming from a robust terminal hair → wispy vellus-like hair)

- Hairs are cycling more rapidly from anagen phase → telogen phase (“**catagen/telogen shift**”)
- Both processes contribute to the ↑ in fibrous streamers seen in androgenetic alopecia
- Note: ↑↑fibrous streamers are also seen in **alopecia areata** and **trichotillomania/traction alopecia**
  - In these diseases the massive catagen/telogen shift is primarily responsible for the dramatic increase in streamers

### Treatment

- Only minoxidil and finasteride are FDA approved for androgenetic alopecia
  - **Topical minoxidil 2% or 5%**
    - Lengthens anagen phase and ↑blood flow
    - Regrowth most effective on **vertex scalp** (> frontal scalp); takes at least 4 months and must be continued indefinitely for hair retention

**Table 3-56.** Dermatoses of Pregnancy

Disorder	Onset	Appearance	Treatment/Course	Risk to Fetus	Interesting Facts
Pemphigoid gestationis (herpes gestationis)	Typically <b>second or third trimester</b> or immediately post-partum	Pruritic papules/plaques that → blisters/bullae mainly on trunk ( <b>does NOT spare umbilicus</b> )	Topical or systemic corticosteroids depending on severity (taper once blisters resolve) Spontaneously resolves but may flare/recur around delivery, with menstruation, or OCPs May take weeks to months after delivery to entirely resolve Typically <b>recurs in future pregnancies</b> (more severe/earlier)	<b>↑risk prematurity and SGA</b> Baby may have mild transient pemphigoid lesions Risks to fetus correlate with dz severity	May occur with <b>choriocarcinoma</b> ↑ risk of Graves' disease Due to IgG1 autoantibodies against <b>BP180 NC-16A segment (DIF with linear C3 along perilesional BMZ)</b> Strongly a/w <b>HLA-DR3 and DR4</b>
Polymorphic eruption of pregnancy	<b>Third trimester</b> or immediately post-partum	Urticarial, pruritic papules/plaques which prefer striae distensae ( <b>sparers umbilicus</b> ) Usually spares face/extremities	Resolves over 4 wks Topical steroids and antihistamines may help Typically does not recur	None	Mainly seen in <b>primiparous women</b> ↑risk in <b>multiple-gestation pregnancies</b>
Intrahepatic cholestasis of pregnancy	Third trimester	<b>Extreme generalized pruritus without primary rash</b> Worse at night Bad on palm/sole Excoriations/ prurigo typically seen on extensor surfaces Jaundice in 10%	MUST ↓ serum bile acid levels – oral <b>ursodeoxycholic acid</b> May recur in future pregnancies and can flare with OCPs May have steatorrhea and vitamin K deficiency → postpartum hemorrhage Pruritus resolves shortly after delivery	<b>↑risk of premature birth, intrapartum fetal distress, stillbirth</b> Risks correlate with bile acid levels (i.e., >40 μmol/L)	↑total serum bile acid levels (>11 μmol/L) due to ↓ excretion
Atopic eruption of pregnancy (prurigo of pregnancy)	Usually first or second trimester	Ecematous or papular eruption usually in typical sites (e.g., flexural surfaces) typically in pts with <b>atopic history</b> May be flare of pre-existing dermatitis or first time they have had dermatitis (80%)	Treatments: topical steroids, emollients, antihistamines, UVB for symptom control Usually recurs with future pregnancies	None	Most have ↑IgE May be Th2 mediated Most common pruritic disorder of pregnancy
Impetigo herpetiformis	Usually third trimester	Generalized <b>pustular psoriasis</b> starting in flexures (groin mainly)	Supportive, prednisone Resolves with delivery typically Recur with future pregnancies and OCPs	<b>Placental insufficiency, stillbirth, neonatal death</b> in bad disease	<b>a/w hypocalcemia</b> and ↓vitamin D Mom may have cardiac/renal failure

- Men: 5% solution shown to be 45% more effective than 2% solution
- Women: 2% solution almost as effective as 5% and has ↓risk of unwanted facial hair growth
- **Finasteride** 1 mg PO daily (**type II 5α-reductase inhibitor**)
  - Only approved for use in males
  - In pregnant females → **risk of abnormal male genitalia in fetuses**
- **Dutasteride** 0.5 mg PO daily (**type I and type II 5α-reductase inhibitor**)
  - Appears to be more effective than finasteride (JAAD 2014 large RCT comparing finasteride and dutasteride)
  - Not yet FDA approved
  - Mnemonic: “**DUtasteride = DUal action**” (inhibits both types I and II)
- Antiandrogens: spironolactone, cyproterone acetate (women only)
- Low level light/laser therapy
- Hair transplantation

**Box 3-7.** Common Causes of Telogen Effluvium

- Thyroid abnormality
- Iron deficiency
- Postpartum/pregnancy
- Drugs – OCPs, retinoids, anticoagulants, anti-thyroid, anticonvulsants, interferon-α, heavy metals, beta-blockers
- Severe stress
- Hospitalization or surgery
- High fever
- Severe illness
- Malnutrition (e.g., ↓protein, ↓iron)

**Telogen effluvium (TE)***Clinical features*

- ↑shedding due to telogen shift in response to stressor
- Normally lose about 100–150 hairs/day, but in TE may lose >150
- Usually occurs 3 to 4 months after inciting cause (see [Box 3-7](#))

- Usually **temporary**; should subside in 6 to 12 months after the inciting factor corrected
  - Occasionally chronic, with inciting factor in some women
- Overall thinning and ↓density of scalp hair
- **Positive hair pull test** (> 4–6 telogen hairs released out of 40 pulled) – will see telogen hairs on hair mount

#### Histology

- Mild ↑percentage of total hairs in catagen/telogen phase (“catagen/telogen shift”):
  - >20%, but less than 50% → indicative of TE (vs <15% in normal scalp)
  - >50% → indicative of alopecia areata, trichotillomania/traction alopecia
- Normal total number of hairs

### Anagen effluvium

- See [Drug Reactions](#) section

### Trichotillomania

- Hair-pulling impulse control or obsessive compulsive disorder
- p/w large, irregular/geometric areas of alopecia (scalp > eyebrows > eyelashes > genital hair) with coexistent areas of completely normal, uninvolved scalp
  - Affected areas contain hair of **varying lengths**
- a/w **trichophagy** (chewing and swallowing of hair) → may cause intestinal obstruction and **trichobezoars**
- **Female > male** (5:1)
- Average age of onset: 8 yo (boys), 12 yo (girls)
  - Histopathology: **huge “catagen/telogen shift”** (↑↑↑catagen/telogen hairs; often >50% of hairs in catagen or telogen phase), **pigmented hair casts**, empty anagen follicles (due to hair shafts being pulled out), **trichomalacia** (distorted hair shafts), and hemorrhage
- Trichoscopy: multiple broken hairs of different lengths and shapes without perifollicular changes
- Confirmatory test: **hair growth window**
  - During repeated shaving of a specific area, hair of normal density regrows (since hairs are too short to manipulate)
- Rx: behavior modification therapy, **clomipramine** (ToC), SSRIs; **prognosis better in younger children** than older children/adolescents

### Alopecia areata (AA)

#### Pathogenesis

- Loss of immune privilege
- Autoreactive cytotoxic CD8+ T-cells target hair follicle antigens
- Type 1 cytokines (IL-2, IFN-γ, and TNF-α)
- One quarter patients with **family history**

#### Clinical features

- Round patches of non-scarring hair loss (follicular ostia visible)
  - **Alopecia totalis**: complete scalp hair loss
  - **Alopecia universalis**: complete scalp and body hair loss
  - **Ophiasis pattern**: band-like loss across occipital and temporal scalp; **poor prognostic factor**
  - **Sisalapho pattern** is opposite where there is hair growth in these areas, but loss of hair in other areas
- **Regrowth hair may be gray or white**
- Can have longitudinal lines of **regular nail pitting** and **trachyonychia**
  - Poor prognostic factor
- Dermoscopy: short **“exclamation point” hairs** and perifollicular yellow dots (small in size vs larger in discoid lupus erythematosus)
- Can be chronic/relapsing and can occur at any age (>5 year duration = poor prognostic factor)
  - **Worse prognosis: childhood or diffuse patterns**
- Associated with:
  - Atopy (**atopic dermatitis = poor prognostic factor**)
  - **Autoimmune thyroid disease**
  - **Vitiligo**
  - Lupus erythematosus
  - IBD

#### Histology

- Classic findings: peribulbar lymphocytic cell infiltrate (**“swarm of bees”**), marked **“catagen/telogen” shift** (↑catagen and telogen hairs), ↑miniaturized hairs (including super small **nanogen** hairs), occasionally trichomalacia +/- pigment casts
  - Note: trichomalacia and pigment casts may be seen in AA → can be confused for trichotillomania
- Elston et al recently described **other helpful clues** in cases lacking classic “swarm of bees”:
  - Lymphocytes (94%), melanin (84%), and eosinophils (44%) in fibrous tracts

#### Treatment

- Topical or intralesional corticosteroids
- Topical minoxidil 2%/5%
- Topical allergens (squaric acid, DNCP, and DPCP)
- Phototherapy
- Systemic corticosteroids

### Temporal triangular alopecia

- Presents at birth or within first decade
- Temporal scalp with **areas lacking terminal hairs** (only fine vellus hairs present)
- Normal total number of hairs within affected area
- Persists throughout life

### Congenital atrichia with papules

- Inherited defect in **Hairless gene** or vitamin D receptor
- p/w **failure to regrow almost all their hair** after shedding of their initial hairs after birth
- Also see **follicular cysts and milia** later in life

## Cicatricial (scarring) alopecia

### General points

- Absence of follicular ostia + hair loss
- It is important to either obtain two biopsies (one for horizontal and one for vertical sections), or to specify to your dermatopathologist whether you are suspecting scarring vs non-scarring alopecia
  - Vertical sections: **best for scarring alopecias**; does not show you many follicles though, so it is a poor method for non-scarring alopecias (except maybe alopecia areata)
  - Transverse/horizontal sections: show all follicular units in specimen → **best method for non-scarring alopecias**; can also be used for scarring alopecias but most dermatopathologists prefer vertical sections for this purpose, since the epidermis is also visible (helpful particularly for DLE vs LPP)

### Primary cicatricial alopecia

- Hair follicle is the inflammatory target
- Classified by type of inflammation ([Table 3-57](#))

### Secondary cicatricial alopecia

- Hair follicle is “innocent bystander” (e.g., burns, radiation dermatitis, skin cancer, sarcoidosis, amyloidosis, and necrobiosis lipoidica)

## Central centrifugal cicatricial alopecia

### Epidemiology

- F > M; African descent

### Pathogenesis

- a/w use of **chemical relaxers, hot combs**, traumatic hairstyles, and pomades

### Clinical features

- Destructive, chronic, and progressive scarring hair loss
- Scarring starts on **vertex scalp**, then **spreads centrifugally**, with doll hairs present
  - Mildly tender

### Treatment

- STOP traumatic hair care practices
- Long term TCN agent therapy
- Topical or intralesional corticosteroids

**Table 3-57.** Cicatricial Alopecias

Lymphocytic	Neutrophilic	Mixed
DLE	Folliculitis decalvans	Acne keloidalis
LPP	Dissecting cellulitis	Erosive pustular dermatosis
Frontal fibrosing alopecia		Acne necrotica
Pseudopelade of Brocq		
CCCA		
Alopecia mucinosa		
Keratosis follicularis spinulosa decalvans		

### Histology

- Premature desquamation of inner root sheath
- Concentric lamellar fibroplasia
- Eccentric thinning of ORS
- Variable lymphocytic perifollicular inflammation (usually not as dense or lichenoid as LPP)
- Polytrichia (fusion of follicular infundibulae) = histologic correlate to “doll hairs”

## Lichen planopilaris

### Epidemiology

- Most common in middle-aged **Caucasian females**

### Clinical findings

- Inflammatory; scarring hair loss, with itching and burning
- Scattered patches of **perifollicular erythema, scaling, and scarring**
- 50% can have skin and nail LP findings
- Frontal fibrosing alopecia
  - Distinct clinical variant w/ similar histopathologic findings
  - Most common in postmenopausal Caucasian women
  - Progressive **frontal hairline recession** w/ atrophic scarring and perifollicular papules
  - **Eyebrow loss** (helpful clue)
- Graham-Little syndrome
  - a/w LPP
  - Scarring hair loss on scalp
  - Non-scarring hair loss of axilla and pubic areas
  - Keratosis pilaris-like spinous follicular papules on trunk

### Histology

- Dense **lichenoid interface dermatitis** of follicular epithelium at the level of the **infundibulum** w/ cytooid bodies, pigment incontinence, and dermal/perifollicular fibrosis (scar)
  - No interface dermatitis seen at DEJ (vs present in DLE)
  - Lacks superficial and deep PV/PA inflammation (vs DLE)
- DIF may show cytooid bodies + shaggy fibrin deposition at DEJ

### Treatment

- Oral antimalarials
- Topical, oral, and/or intralesional corticosteroids
- PPAR-γ antagonists (e.g., pioglitazone)
- MTX, cyclosporine, acitretin, and MMF
- For frontal fibrosing alopecia, finasteride/dutasteride are good options

## Acne keloidalis nuchae

### Clinical findings

- Firm, perifollicular papules on **occipital scalp and posterior neck** that can become keloidal and coalesce into plaques



- Most common in **blacks**
- Eventual scarring alopecia

#### Histology

- Mixed (lymphoplasmacytic and neutrophilic) perifollicular inflammation at the isthmus and lower infundibulum
- Lamellar fibroplasia
- Loss of sebaceous glands

#### Treatment

- Topical or intralesional corticosteroids
- Systemic and topical antibiotics
- Surgical removal

### Dissecting cellulitis of the scalp (perifolliculitis capitis abscedens et suffodiens)

#### Epidemiology

- Most commonly young adult **black men**

#### Clinical features

- Numerous inflammatory nodules forming **boggy, intercommunicating, purulent sinuses** with drainage → overlying scarring and alopecia (Fig. 3-91)
- Favors **vertex and occipital scalp**
- **Follicular occlusion tetrad**: acne conglobata, hidradenitis suppurativa, dissecting cellulitis, and pilonidal cysts

#### Histology

- Dense, pandermal neutrophilic inflammation with abscess formation, scarring, and sinus tracts
- Later inflammation may be lymphoplasmacytic or mixed, rather than purely neutrophilic

#### Treatment

- Very difficult to treat!
  - Options: **oral isotretinoin**, intralesional corticosteroids, **oral antibiotics** (e.g., TCNs, clindamycin/rifampin (if positive for *S. aureus*)), I&D,



**Figure 3-91.** Dissecting cellulitis of the scalp. (From Lebwohl MG, et al. Treatment of Skin Disease: Comprehensive Therapeutic Strategies, 4th ed. Elsevier. 2013)

excision, TNF- $\alpha$  inhibitors, intralesional injection of sinus tracts w/ sclerosing agents

### Folliculitis decalvans

#### Epidemiology

- Most commonly in **black men**

#### Clinical features

- Discrete, **crusted inflammatory papulopustules** arising in **crops** on vertex scalp → cicatricial alopecia
- Often colonized with *S. Aureus*

#### Histology

- Dense **neutrophilic** perifollicular inflammation at upper portion of follicles (same level as in LPP)
- Later inflammation often mixed (neutrophilic + lymphoplasmacytic)

#### Treatment

- Topical clindamycin, topical corticosteroids, and selenium sulfide shampoo
- Oral TCNs, rifampin + clindamycin

### Traction alopecia

#### Epidemiology

- Most commonly in **black females**

#### Pathogenesis

- Tension from repeated **traumatic hairstyles** (e.g., tight ponytails, braids, weaves, extensions, and rollers)

#### Clinical features

- Hair loss/thinning along the frontotemporal hairline
- Biphase in nature – initially temporary, but can become permanent
- “Fringe sign” = preservation of frontal rim of hair

#### Histology

- Non-scarring phase (early): histology same as trichotillomania
- Scarring phase (late): columns of connective tissue replace hair follicles; markedly decreased number of terminal hairs

### Hair shaft abnormalities

- Many of these disorders have been discussed elsewhere but are briefly reviewed here
- Hair shaft abnormalities are divided into those that are associated with **increased hair fragility** and those that are **not associated with increased hair fragility**
- See [Table 3-58](#)

### Hypertrichosis and hirsutism

#### Hypertrichosis

- Definition: excessive hair growth
  - vs hirsutism: female with ↑ terminal hair growth in a “male distribution” (upper lip, cheeks, central chest)

**Table 3-58.** Structural Hair Abnormalities

Disease	Affected Gene/Pathogenesis	Findings
<b>Structural Hair Abnormalities with Increased Hair Fragility</b>		
Bubble Hair	<b>Traumatic heat styling</b>	Young women with a localized area of uneven, fragile hairs Light microscopy: <b>hair shafts w/ large, irregularly spaced “bubbles”</b> that expand and thin the hair cortex → hair fractures at the site of larger bubbles
Monilethrix	AD inheritance: hair cortex-specific keratin genes <b>KRT86</b> (most often; previously referred to as <i>hHb6</i> ) and <b>KRT81</b> ( <i>hHb1</i> ) AR inheritance: <b>Dsg4</b>	p/w normal-appearing hair at birth Within first few months of life, hairs are replaced by <b>short, fragile, brittle hair w/ perifollicular erythema and follicular hyperkeratosis</b> Scalp usually only site affected (occasionally eyebrows, eyelashes) Hairs have <b>uniform elliptical nodes</b> of normal thickness and <b>intermittent abnormal constrictions</b>
Pili torti	<b>Menkes kinky hair disease:</b> XLR, <b>ATP7A</b> (→ defective copper transport) <b>Bjornstad/Crandall syndrome:</b> AR, BCS1L gene Netherton's: <b>SPINK5</b> gene (encodes serine protease inhibitor LEKT1) Urea cycle defects ( <b>citrullinemia, argininosuccinic aciduria</b> ) Acquired pili torti: <b>anorexia nervosa</b> and <b>oral retinoids</b>	Flattened shaft and twisting of hair fiber on its own axis <u>Inherited forms:</u> hair abnormal from birth, or normal at birth and then during infancy becomes replaced by brittle and fragile hair; body hair also sparse to absent; no treatment exists but improves at puberty Menkes: <b>pili torti</b> (sparse, lusterless hair on scalp/brows/lashes) and <b>trichorrhexis nodosa</b> ; growth failure, wormian bones/fractures; neurologic abnormalities (seizures, lethargy, <b>mental/psychomotor retardation</b> , hypertonia), <b>“Cupid's bow”</b> upper lip; <b>doughy skin; diffuse hypopigmentation</b> (tyrosinase requires copper!) Bjornstad: pili torti + <b>hearing loss</b> <b>Crandall syndrome</b> = Bjornstad syndrome + <b>hypogonadism</b> (mnemonic “Crandall's = Cranberry balls”) Bazex-Dupre-Christol: pili torti, <b>basal cell carcinomas, milia, follicular atrophoderma</b> (dorsal hands/feet, face, elbows, knees), <b>hypohidrosis, hypotrichosis</b> (+/- pili torti)
Trichorrhexis invaginata (“bamboo hair”)	Netherton syndrome: <b>SPINK5</b> gene (encodes serine protease inhibitor LEKT1)	Netherton's: ichthyosis linearis circumflexa, atopy and hair abnormality (trichorrhexis invaginata, trichorrhexis nodosa) Hair abnormality arises in infancy, p/w <b>short, sparse and very fragile hair</b> Hair breakage points arise at intussusceptions of distal shaft (“ball”) into proximal shaft (“socket”) May also see proximal shafts with a <b>golf tee-shaped appearance</b>
Trichorrhexis nodosa	<u>Congenital:</u> <b>argininosuccinic aciduria</b> (AR, arginosuccinate lyase) or <b>citrullinemia</b> (AR, arginosuccinate synthetase) most commonly; also may see in Menkes, trichothiodystrophy, Netherton's <u>Acquired (three variants):</u> (1) <i>proximal</i> trichorrhexis nodosa: arises in patients after years of hair straightening (2) <i>distal</i> trichorrhexis nodosa: due to acquired, cumulative, cuticular damage (3) <i>circumscribed</i> trichorrhexis nodosa: affects scalp, moustache, or beard	<b>Most common</b> of all the structural hair abnormalities Characterized on light microscopic examination by a hair shaft fracture w/ adjacent fragments splaying out, resembling the <b>ends of two brushes pushed against each other</b> Citrullinemia: pili torti, trichorrhexis nodosa, hyperammonemia, lethargy, vomiting, seizures, CNS symptoms Argininosuccinic aciduria: pili torti, trichorrhexis nodosa, hyperammonemia, vomiting, seizures Neonatal form more severe – failure to thrive, hepatomegaly, lethargy Adult-onset form less severe but still have mental retardation and ataxia Treat with restricted protein diet + arginine supplementation; liver transplant may be curative
Trichothiodystrophy	AR disorder characterized by <b>sulfur-deficient hair</b> ; due to several related genetic defects involving <b>TFIIH/XPD-XPB complex</b>	Microscopy: transverse fractures ( <b>trichoschisis</b> ), and <b>alternating light and dark bands under polarizing light</b> Clinical: may be isolated finding or <b>a/w PIBIDS</b>
<b>Structural Hair Abnormalities without Increased Hair Fragility</b>		
Acquired progressive kinking of the hair	<b>Can be early sign of AGA</b>	Young men develop progressively curly, frizzy, lusterless hair in androgenetic areas → progresses to AGA
Loose anagen hair syndrome	Faulty cornification of inner root sheath → interference with normal interdigitation of the IRS cuticle and the hair cuticle → poorly-anchored anagen hairs	<b>Classic presentation: young girl w/ short blond hair that seldom needs to be cut</b> ; see diffuse or patchy alopecia No ↑ hair fragility Anagen <b>hairs can be easily and painlessly pulled</b> from the scalp Hair microscopy: ruffled proximal cuticle, absence of root sheath, and a bent matrix
Pili annulati (“ringed hair”)	Sporadic or AD	Ringed hair with <b>light and dark bands</b> due to air-filled spaces <b>Do NOT need polarized light to see (vs trichothiodystrophy)</b>
Pili bifurcati	–	Multiple bifurcations of the hair shaft; each ramus has its own cuticle
Pili multigemini	–	Multiple hair shafts arise from one papilla Each hair fiber has its own IRS but all the fibers are surrounded by a common ORS Most commonly occurs on <b>beard area</b>
Pili trianguli et canalculi (aka “spun glass hair,” “uncombable hair”)	–	Hair w/ <b>“spun glass” appearance</b> and <b>difficulty with combing</b> Due to light reflection off of flattened hair surfaces; <b>hairs have triangular shape</b> on cross-section w/ <b>longitudinal grooves</b> best seen by scanning electron microscopy
Wooly hair syndromes	<u>Naxos disease</u> (diffuse non-epidermolytic PPK, <b>RVH</b> and wooly hair): <b>plakoglobin</b> mutations <u>Carvajal syndrome</u> (striate epidermolytic PPK, <b>LVH</b> , wooly hair): <b>desmoplakin</b> mutations	Microscopy: elliptical cross-sections, axial twisting, +/- trichorrhexis nodosa Mnemonic: “Carvajal has <b>LVH</b> ” (vs RVH in Naxos)
Wooly hair nevus	–	Well-defined, circumscribed patch of wooly hair

(Adapted from Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- Vellus more so than terminal hairs
- May be generalized or localized; also may be divided into congenital vs acquired
- Most testable forms:
  - Acquired hypertrichosis lanuginosa
    - Paraneoplastic disease a/w lung, colon, and breast cancer
    - Lanugo hair quickly forms over entire body, especially face → “simian” appearance
  - Acquired generalized hypertrichosis
    - Slow growth of terminal hairs of medium thickness
    - Most prominent on forehead, temples, trunk, and flexor extremities
    - Reversible
    - Medication-induced (most common): minoxidil, phenytoin, and cyclosporine
    - Other causes: hypothyroidism, POEMS, porphyria, advanced HIV, dermatomyositis and SLE, and anorexia nervosa
  - Acquired trichomegaly (primarily of eyelashes)
    - May be a/w HIV
    - May be a/w meds (most common cause of acquired): cyclosporine, phenytoin, minoxidil, EGFR inhibitors, topiramate, tacrolimus, interferon- $\alpha$ , danazol, prostaglandin F-2 $\alpha$ , and topical latanoprost/bimatoprost
  - Localized hypertrichosis
    - Causes: Becker’s nevus, melanocytic nevi, spinal dysraphism w/ “hair collar sign,” aplasia cutis w/ “hair collar sign,” trauma (areas of chronic rubbing, or fractured limbs w/ plaster casts), or medication-induced (prostaglandin analogues, PUVA sites)

## Hirsutism

- Definition: ↑ terminal hair growth in a female, with a “male pattern” (e.g., upper lip, cheeks, central chest, suprapubic area, back)
- Common; affects 5%–10% of women of reproductive age
- Related to ↑androgens (from ovary or adrenal glands) or end-organ sensitivity to androgens from adrenal glands and ovaries
  - DHEA-S = marker for adrenal androgens
  - $\Delta$ -4-androstenedione = marker for ovarian androgens
- Useful rules of thumb:
  - Rapid onset hirsutism w/ fast evolution → tumor (adrenal, ovarian, or pituitary)
  - Hirsutism limited to areola, lateral face/neck → ovarian source most likely
  - Central hirsutism (pubic triangle to upper abdominal area and sternal area up to chin) → adrenal most likely
  - Lateral face and back → iatrogenic hirsutism
- Labs: recommendations vary, but experts recommend checking total testosterone, DHEA-S, 24 h urine cortisol,  $\Delta$ -4-androstenedione, SHBG, prolactin, and 3- $\alpha$ -androstenediol glucuronide (metabolite of DHT)
  - May add on 17-OH-progesterone (elevated in setting of CAH due to 21-hydroxylase deficiency) and other

additional labs depending on results of these initial studies (Fig. 3-92)

- Four major causes:
  - PCOS (accounts for majority):
    - Characterized by infertility, large polycystic ovaries, secondary amenorrhea, or menstrual cycle irregularities
    - a/w hirsutism in 90%; also a/w acne (70%), obesity (50%), androgenetic alopecia, acanthosis nigricans, and insulin resistance
    - Labs: ↓FSH, ↑LH, LH:FSH ratio >3, ↑testosterone, ↑estrone, ↓SHBG, and normal DHEA-S
  - Congenital adrenal hyperplasia (CAH)
    - May be due to a variety of enzyme deficiencies but 95% of CAH is due to 21-hydroxylase deficiency
      - ◆ Classic “salt-wasting form:” p/w salt-wasting in first 2 weeks of life w/ dehydration and electrolyte abnormalities (due to absence of cortisol); female infants have ambiguous genitalia and virilization; both sexes have premature growth of axillary and pubic hair during early childhood; ↑17-OH-progesterone (build-up due to lack of 21-hydroxylase function), ↑DHEA-S, ↑↑ACTH, and normal or mildly elevated testosterone
    - Check 17-hydroxyprogesterone and ACTH stimulation test to r/o late onset CAH (partial deficiency of 21-hydroxylase or other enzymes)
  - Neoplastic
    - If virilization also present or very high testosterone (>200 ng/dL) → neoplastic etiology most likely (e.g., arrhenoblastomas, Leydig cell tumors)
    - ↑↑↑testosterone but normal DHEA-S → ovarian tumor
    - ↑↑testosterone and ↑↑↑DHEA-S → adrenal tumor
  - Constitutional hirsutism
    - No hormonal abnormalities present
    - More common in certain ethnicities (e.g., Southern and Eastern European, Southwest Asian)
- Treatment
  - Antiandrogens (e.g., spironolactone, leuprolide, flutamide, finasteride), OCPs, topical eflornithine, metformin, depilatory methods/agents, and laser hair removal

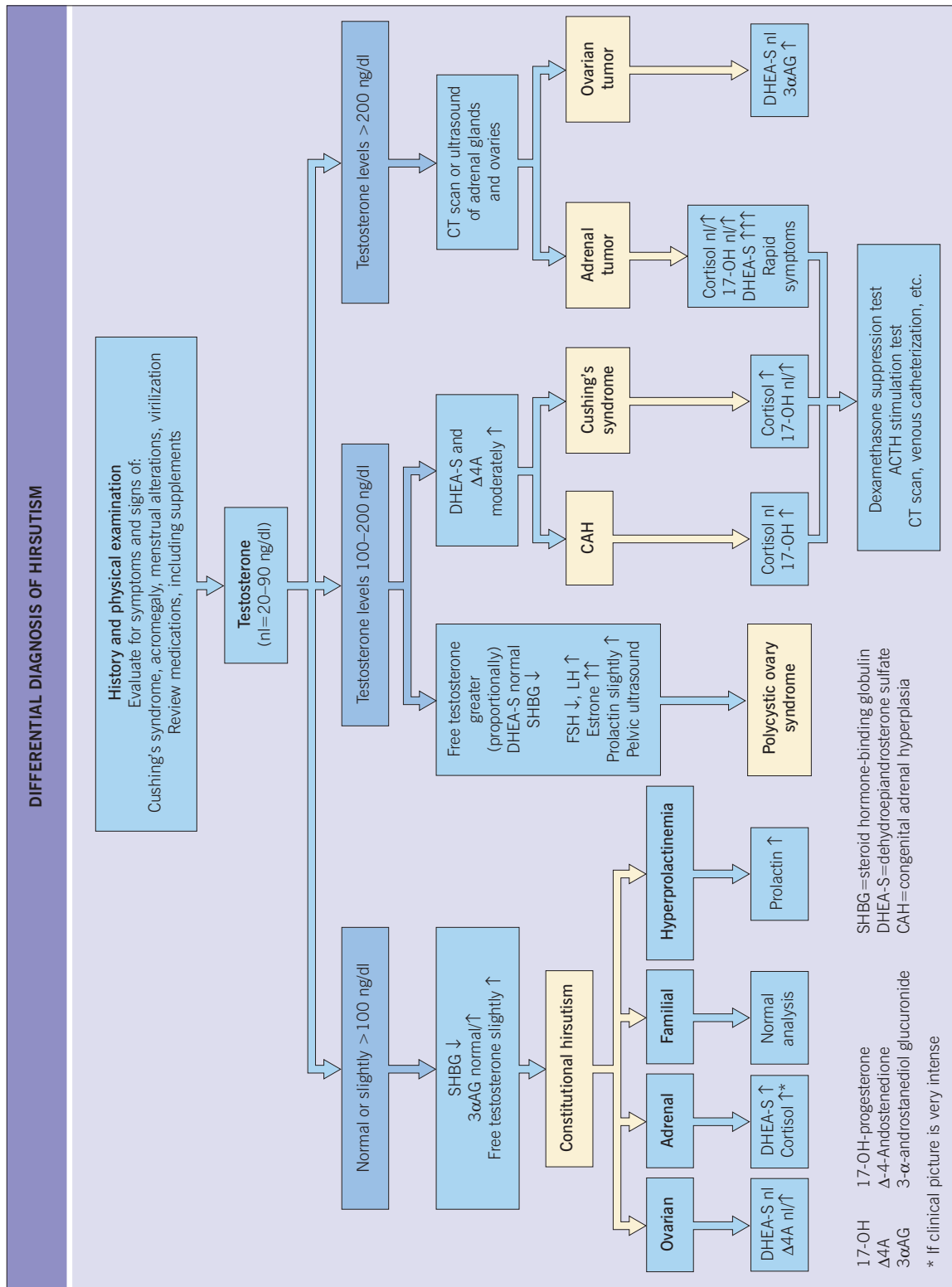
## Nail disorders

- Anatomy of the nail (Fig. 3-93)
- Disturbances of nail sites can → various clinical manifestations (Fig. 3-94) and Table 3-59

## Mucosal disorders

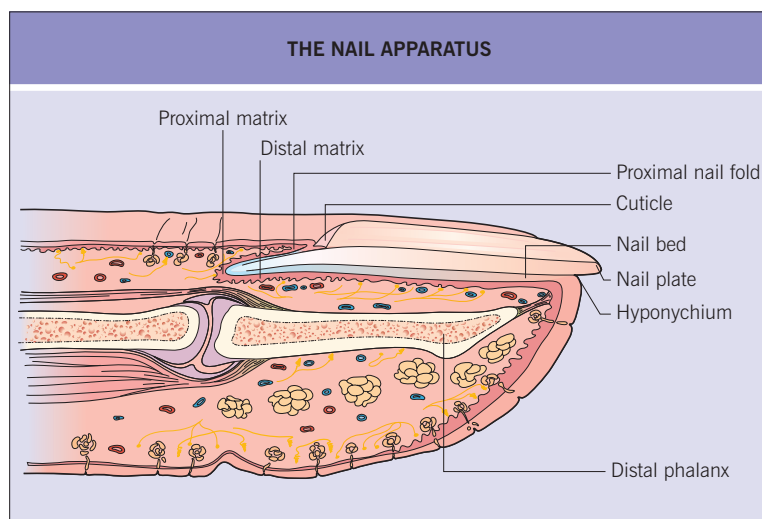
- Discussed in Table 3-60

text continued on p. 203

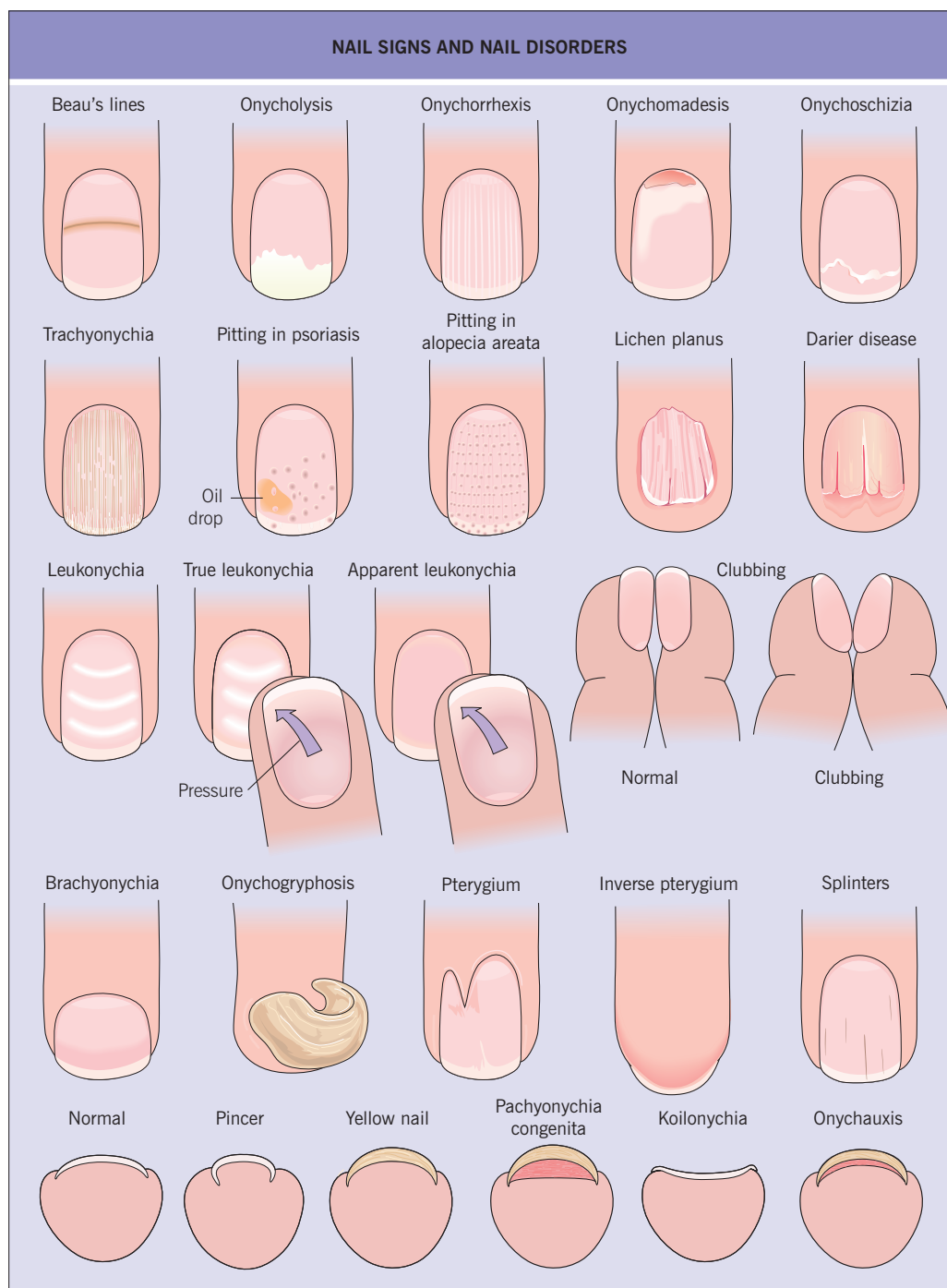


**Figure 3-92.** Differential diagnosis of hirsutism. The optimum time to assess circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels is 3–5 days after cessation of menses. (From Bologna JL, Jorizzo JL, Rapini RP: Dermatology, 3rd Ed. Elsevier, 2012)





**Figure 3-93.** Schematic drawing of the nail apparatus in longitudinal section. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 3-94.** Nail signs and disorders. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 3-59.** High Yield Nail Disorders

Nail Sign/Disorder	Cause/Site of Injury	Associations
Beau's lines	Matrix (proximal) – <b>temporary stoppage of growth</b>	Usually due to mechanical trauma or skin diseases of proximal fold; also <b>chemotherapy</b> , stress on body (e.g., childbirth), <b>systemic illness</b> , major injury
Onychomadesis	Matrix (proximal) – temporary stoppage of growth	Same as above; also seen with <b>Coxsackievirus</b> infection (hand-foot-mouth disease)
Pitting	Matrix (proximal)	<b>Psoriasis</b> <b>Alopecia areata</b> (geometric, regularly distributed grid-like small superficial pits)
Onychorrhexis (brittle nails)	Matrix	Lichen planus Chronic wet work, frequent nail polish use, eating disorders
Trachyonychia (sandpaper nails)	Matrix	<b>Alopecia areata</b> (children > adults) Lichen planus, psoriasis, and other autoimmune processes
True leukonychia	Matrix	Punctate: usually from trauma in kids Striate: fingernails in women from <b>manicures</b> ; great toenails from shoe trauma; <b>Mee's lines</b> from arsenic and thallium Diffuse: rare – may be congenital
Koilonychia	Matrix	Normal in kids; in adults may be associated w/ <b>iron deficiency</b> (e.g., <b>Plummer-Vinson syndrome</b> )
Onycholysis	Nail plate detachment (distal)	<b>Psoriasis</b> <b>Onychomycosis</b> Trauma (e.g., great toenails with shoes), drugs (e.g., <b>photo-onycholysis w/ TCN/fluoroquinolones/chloramphenicol/ psoralens + UV</b> ) Systemic causes (e.g., thyroid issues)
Onychauxis	Subungual hyperkeratosis → thickened nail	Causes include psoriasis, onychomycosis, eczema
Onychocryptosis (ingrown nail)	Excess lateral nail growth into nailfold → pseudo-foreign body reaction/ inflammation	None, but may be mimicked by periungual pyogenic granuloma (which may be due to various meds like isotretinoin, protease inhibitors, and EGFR inhibitors)
Apparent leukonychia	Nail bed edema (white color that <b>fades w/ pressure</b> )	Chemotherapy Chronic hypoalbuminemia ( <b>Muehrcke's nails</b> = transverse white bands parallel to lunula) Liver cirrhosis ( <b>Terry's nails</b> = leukonychia of most of nail plate) Chronic renal disease w/ hemodialysis ( <b>half and half nails</b> – leukonychia of half nail plate)
Longitudinal erythronychia	Erythema from matrix to distal onychodermal band	Seen in inflammatory conditions (e.g., lichen planus, <b>Darier disease</b> )
Splinter hemorrhages	Damage to nail bed capillaries	Distal (usually from <b>trauma</b> , psoriasis, onychomycosis) Proximal ( <b>endocarditis</b> , vasculitis, trichinosis, APLS) – rarer
Longitudinal melanonychia	Melanin within nail plate (e.g., melanocyte activation or hyperplasia)	Matrix melanoma/nevus Non-melanocytic tumors Melanocyte activation (2/2 racial (e.g., <b>African Americans</b> ), HIV, drugs (e.g., <b>AZT</b> , antimalarials, minocycline, gold), Addison's disease, Peutz-Jegher/ <b>Laugier-Hunziker</b> syndrome, onychomycosis ( <i>T. rubrum</i> , <i>Scytalidium spp.</i> ))
Hutchinson's sign	Pigmentation in proximal nail fold w/ longitudinal melanonychia	May be <b>sign of nail melanoma</b> , particularly in adults
Green nail syndrome	Green staining of nail plate due to <b>pyocanin</b> from <b>Pseudomonas</b>	Factors → infection are wet work (e.g., barbers, dishwashers), nail trauma, harsh exposures of note, <b>black nails may be caused by Proteus mirabilis</b> or <i>Trichophyton rubrum</i>
Red lunulae	Erythema of lunulae	<b>SLE</b> , <b>alopecia areata</b> , <b>rheumatoid arthritis</b> , <b>dermatomyositis</b> , <b>cardiac failure</b> , cirrhosis, lymphogranuloma venereum, psoriasis, vitiligo, chronic urticaria, LS&A, <b>carbon monoxide</b> poisoning, COPD
Brachyonychia	Shortening of distal phalynx → racquet thumb	Congenital finding– may be seen in <b>Rubinstein-Taybi</b> syndrome
Nail-Patella syndrome	<b>Mutation of LMX1B</b> (autosomal dominant)	Manifestations include: nail abnormalities (radial side of thumbs most commonly – <b>triangle-shaped lunula</b> may occur), bone findings (e.g., <b>absent/ underdeveloped patellae</b> , <b>iliac horns</b> ), <b>nephropathy</b> /renal insufficiency, <b>Lester iris</b> (pigmentation of pupillary margin of iris)
Clubbing	Soft tissue growth in distal digit → curved, enlarged nail plate	Various causes, but <b>pulmonary</b> most common in acquired type; HIV is another reported cause
Yellow nail syndrome	Arrest in nail growth → yellow color, absent cuticle, thickening/curved (transversely and longitudinally)	a/w <b>lymphedema</b> , <b>pleural effusions</b> , <b>bronchiectasis</b> , chronic pulmonary infection/sinusitis
Acute paronychia	<b>S. aureus</b> or <i>S. pyogenes</i> infection → inflamed tender digit	Usually due to trauma Treat with drainage of abscess and treatment of infection
Chronic paronychia	Inflammation of proximal nail fold → fingernail issues and cuticle loss	Usually due to continuous contact exposure/ <b>wet work</b> (e.g., food handlers) <b>Secondary infection with Candida</b> common
Habit-tic deformity	Due to manipulation of mid-cuticle of thumb → central longitudinal depression	<b>Median canaliform dystrophy</b> may be subtype with “ <b>inverted fir tree</b> ” appearance

Continued

**Table 3-59.** High Yield Nail Disorders—cont'd

Nail Sign/Disorder	Cause/Site of Injury	Associations
Pincer nails	Overcurvature of nail plate	Can → pain due to pinching of distal nail bed Hereditary vs acquired (trauma from shoes) <b>Lateral matricectomy is ToC</b> ; r/o subungual exostosis
Onychomatricoma	Tumor → thickening of nail plate w/ multiple longitudinal hollow spaces (contain tumor)	Middle-aged patients on fingernails typically Frontal view of nail: <b>holes in thick free margin</b> Yellow-white thick longitudinal nail portion w/ splinter hemorrhages
Subungual exostosis	Subungual bony growth → nodule → nail plate elevation	Usually due to trauma in young patients; most commonly on hallux <b>X-ray</b> confirms diagnosis
Myxoid cysts (digital mucous cyst)	Outpouching of DIP joint space via a tract	<b>Most common nail tumor</b> Classic appearance is small <b>translucent nodule close to proximal nail fold</b> with nail plate groove distally
Pterygium unguis	Scarring between eponychium and matrix	Classically seen in <b>lichen planus</b>
Pterygium inversum unguis	Attachment of distal nailbed to ventral nail plate	a/w CTDs, esp. <b>scleroderma</b>

**Table 3-60.** High Yield Mucosal Disorders

Disorder/Finding	Clinical Findings	Interesting Facts/Treatment
Fordyce granules	Pinpoint white-yellow papules on <b>vermillion and buccal mucosa</b>	Ectopic sebaceous glands like meibomian (eyelids), <b>Montgomery (areolae)</b> , <b>Tyson (labia minora, prepuce)</b>
Geographic tongue	Well-demarcated patches of atrophy with surrounding erythema surrounded by white/yellow scalloped border on dorsal tongue	<b>a/w psoriasis</b> and atopy; histologically looks like psoriasis
Fissured tongue	Grooves on dorsum of tongue which can appear deep	Associated with: <b>Melkersson-Rosenthal syndrome</b> (along w/ recurrent or permanent facial nerve paralysis and swelling of face/lips), Down syndrome, Cowden syndrome
Torus palatinus	Bony prominence in middle of hard palate (normal variant)	
Hairy tongue	Dorsum of tongue with dark hairy-like appearance due to keratin retention → hypertrophic papillae from ↓sloughing color may be due to <b>bacteria</b> (porphyrin production), tobacco, food	Risk factors: <b>bad hygiene, smoking</b> , hot drinks Can treat with tongue scraper +/- dilute H <sub>2</sub> O <sub>2</sub>
Smooth tongue (atrophic glossitis)	<b>Atrophy of papillae</b> → smooth appearance can be tender, sensitive, burning may assume a beefy red appearance	May be due to <b>vitamin deficiency</b> (e.g., B1, B2, B6, B12, iron (e.g., Plummer-Vinson), folate), or other disorders (e.g., Sjogren's syndrome)
Median rhomboid glossitis	Well-circumscribed erythematous smooth area on central dorsum of tongue (in front of <b>circumvallate papillae</b> ; possibly a developmental defect)	<b>a/w oral candidiasis</b> May be sign of HIV infection or DM2 if more extensive Differentiate from herpetic geometric glossitis (geometrically shaped fissured patch on dorsal tongue a/w HSV1)
Necrotizing ulcerative gingivitis	<b>Gingivae are necrotic</b> , painful, swollen, red, bloody, and have ulcerated "punched out" interdental papillae due to <b>mixed bacterial infection</b>	Risk factors: immunosuppression, <b>malnutrition</b> , stress, smoking, poor oral hygiene
Fibroma	Pink smooth papule usually on buccal mucosa usually along <b>bite line</b>	<b>#1 tumor of oral cavity</b> Middle aged women mainly
Cutaneous sinus of dental origin	Sequela of dental caries in which infectious abscess extends to apex of tooth, then medullary bone, then finally oral mucosal surface/facial skin where it drains red eroded papule in adjacent to teeth <b>mandibular &gt; maxillary</b>	
White sponge nevus	White, spongy well-defined small plaques on <b>buccal mucosa</b> most commonly, but can be found in other oral areas	<b>Keratin 4 and 13 mutation</b>
Morsicatio buccarum	White ragged, shredded surface changes of anterior buccal mucosa bilaterally due to <b>habitual chewing</b> of mucosa	
Gingival enlargement (drug)	Gingival growth seen in first year of med use worse if oral hygiene is poor	Culprits: <b>phenytoin, nifedipine, cyclosporine</b> , though other anticonvulsants and CCBs can also cause
Contact stomatitis	Mostly due to <b>cinnamon flavoring</b> and <b>dental amalgam</b> may see erythematous and/or white eroded, ulcerated patches, which may be adjacent to amalgam sites	Histologically, lichenoid mucositis is seen
Recurrent aphthous stomatitis	Painful small oval ulcers – <b>white/grey base with erythematous border</b> , on <b>non-keratinized mucosa</b> Types are <b>minor</b> (most common, ulcers <5 mm), <b>major</b> (ulcers larger (>1 cm), deeper, and last longer) and <b>herpetiform</b> (multiple small grouped ulcers which look like HSV infection)	Multifactorial etiology with a wide differential (r/o vitamin deficiencies, systemic disorders) M > F, teenagers most commonly Topical CS and/or local anesthetics first line, with colchicine or dapsone if needed

**Table 3-60.** High Yield Mucosal Disorders—cont'd

Disorder/Finding	Clinical Findings	Interesting Facts/Treatment
Eosinophilic ulcer of the oral mucosa	Rare self-limited ulceration of posterior <b>tongue</b> > mucosa indurated border with overlying pseudomembrane enlarge quickly, up to 1–2 cm	Plentiful eosinophils on biopsy likely due to trauma; some a/w HIV spontaneous resolution
Orofacial granulomatosis	Chronic swelling of lips ("granulomatous cheilitis" – may be seen in <b>Melkersson-Rosenthal</b> syndrome; upper lips then lower lips), face, and oral region young adults primarily	Non-caseating granulomas on histology May be seen in sarcoidosis or Crohn's disease
Oral leukoplakia/erythroplakia	<u>Leukoplakia</u> = well-defined white patch/plaque Premalignant (to SCC); associated w/ tobacco, alcohol Most commonly on floor of mouth, lateral/ventral tongue, soft palate <u>Erythroplakia</u> = well-defined red patch/plaque <b>Higher likelihood of malignancy</b> (SCCIS, SCC)	Leukoplakia = most common premalignant oral lesion, M > F, peaks at >50 yo Erythroplakia is rare
Mucocele	Soft translucent to bluish papule on mucosa (lower labial mucosa most commonly) Due to rupture of minor salivary gland duct → mucus in the submucosal tissue/pseudocyst formation	
Cheilitis exfoliativa	Desquamative/exfoliative inflammatory condition of lips → red/denuded/tender appearance	1°: upper lip; scaly/crusty 2°: lower lip; may be due to seborrheic dermatitis, atopic dermatitis or other factors
Angular cheilitis (perleche)	Erythema and fissuring involving labial commissures – irritant in nature +/- 2° <i>Candida</i> or staphylococcal infection	RFs: elderly (esp. w/ <b>dentures</b> ), <b>riboflavin deficiency</b> , thumb sucking, Down syndrome, AIDS
Cheilitis glandularis	Enlargement/eversion of <b>lower lip</b> with pinpoint erythema (inflammation of secretory ducts) + <b>sticky mucoid film</b> ; feels nodular due to enlarged glands	<b>Adult men with h/o sun exposure</b> <b>↑SCC risk</b>
Pyostomatitis vegetans	Several to numerous <b>pinpoint yellow pustules</b> (in "serpentine" pattern) with red background → erosion/ulceration ("snail-track" ulcers) Labial, gingival; buccal mucosa most common <b>Deep edematous folds of buccal mucosa</b>	a/w <b>IBD (UC &gt; Crohn's)</b> Treat IBD → improvement of dz M > F, young adults to middle-aged
Zoon's balanitis	Bright red, speckled, well-defined, smooth patches on <b>glans penis</b> (may have "kissing" lesions – e.g., glans of penis and inner foreskin) >> vulva	M > F, middle-aged lichenoid interface dermatitis with <b>↑↑plasma cells</b> <b>Circumcision</b> curative in men

## 3.26 PIGMENTARY DISORDERS

### Disorders of hypopigmentation and depigmentation

#### Vitiligo

##### Epidemiology

- Average age of onset = 20 yo; females acquire disease earlier

##### Pathogenesis

- Multifactorial disease with genetic and non-genetic causes
- Absence of functional melanocytes secondary to **melanocyte destruction**
- Various hypotheses exist for the pathogenesis of vitiligo:
  - An **autoimmune theory** suggests that alterations in cellular or humoral immunity → melanocyte destruction
    - Possibly secondary to cytotoxic activity of autoreactive T-cells against melanocytes
  - Other theories: intrinsic defect in structure/function of melanocytes, dysregulation of the nervous system → melanocyte damage, cytotoxic metabolites (extrinsic or intrinsic), biochemical anomalies (e.g., bipterin pathways), and oxidative stress (e.g., ↓catalase levels)

- Genetics include incomplete penetrance, genetic heterogeneity, and multiple susceptibility loci

##### Clinical features

- **Well-circumscribed, depigmented**, and asymptomatic macules/patches
  - Sites of predilection: fingers, wrists, axillae, groin, genital, and facial (around mouth/eyes)
  - Areas can enlarge over time, slowly, or rapidly
  - Köebner phenomenon
- Can occur anywhere and is often classified as either localized (segmental (primarily in children), focal, or mucosal), **generalized (most common type)**, or universal (>80% of skin)
- Various clinical variants of vitiligo: vitiligo punctuë, inflammatory vitiligo, blue vitiligo, and trichrome vitiligo
- Insidious onset with unpredictable course

##### Associations and clinical DDx

- a/w other autoimmune diseases (**thyroid dysfunction (most common association)**, DM1, Addison's disease, and pernicious anemia), **halo nevi**, alopecia areata, and uveitis
- **Vogt-Koyanagi-Harada syndrome**: bilateral granulomatous uveitis, aseptic meningitis, dysacusia/deafness, poliosis/alopecia, and vitiligo
- **Alezzandrini syndrome**: unilateral facial vitiligo/poliosis with visual/hearing impairment on the same side



- Kabuki syndrome: developmental delay, congenital heart defects, skeletal anomalies/short stature, in addition to autoimmune issues (e.g., vitiligo)

#### Treatment

- Topical steroids, TCIs, topical vitamin D analogs, NB-UVB phototherapy/excimer laser, systemic immunosuppressants, surgical therapies, and depigmentation

#### Prognosis/clinical course

- **Bad prognostic indicators:** mucosal involvement, family history, koebnerization, and non-segmental disease
- **Good prognostic indicators:** recent onset, younger, and lesions of face/neck/trunk
- **Follicular repigmentation** (migration of melanocytes from hair follicles) is typical

### Halo nevus

- Melanocytic nevus with surrounding, well demarcated hypo-/depigmented skin
  - Usually upper back
- On histology, dense band-like infiltrate of lymphocytes and macrophages surrounding nests of melanocytes
- Many halo nevi regress over the several months
- Presence of lesion warrants full skin exam as it can be melanoma marker

### Chemical and physical agent-induced hypopigmentation

- Chemical leukodermas consisting of hypo-/depigmentation of skin/hair can result from various chemical and pharmacologic agents (e.g., **phenols/catechols** and **sulphydryls**)
  - The phenol derivative, monobenzyl ether of hydroquinone → depigmentation
  - Topical steroids, hydroquinone, and imatinib can → hypopigmentation
- Physical injuries from burns, freezing, radiation, lasers, surgery, UV irradiation, and physical trauma can damage melanocytes → hypo-/depigmentation

### Idiopathic guttate hypomelanosis

- ↑incidence with age; more common in skin of color
- Thought to be related to sun exposure, aging, and genetics
- p/w well demarcated asymptomatic hypo-/depigmented macules, especially extremities

### Progressive macular hypomelanosis

- Usually in **darker women from tropical regions**
- Unknown etiology, but *Propionibacterium acnes* may be involved
- p/w ill-defined, hypopigmented macules/patches on trunk/upper extremities, with no scale which can become confluent
- Treatments: benzoyl peroxide, topical clindamycin, and UVA irradiation

### Nevus anemicus

- Pale, typically unilateral area of skin (5–10 cm) with irregular outline
- Present **from birth** and typically on the trunk
- Caused by ↓**blood flow/vasoconstriction in the dermal papilla d/t localized hypersensitivity of blood vessels to catecholamines**; most noticeable when heat or emotional stress causes surrounding vasodilation with diascopy; nevus is no longer visible

### Pigmentary mosaicism

#### Hypomelanosis of Ito

- Hypopigmentation **along Blaschko's lines** d/t mosaicism
- aka linear nevoid hypopigmentation
- Present at birth or early infancy/childhood
- Affects trunk and extremities more commonly; can be unilateral or bilateral
- 30% of patients also have **CNS, MSK, or ophthalmologic abnormalities**

#### Nevus depigmentosus

- Hypomelanotic patches that are well demarcated with irregular borders
- Typically appears in infancy on the trunk with distinct midline demarcation and less distinct lateral borders
- Throughout life it remains stable in size and distribution
- Histopathology: normal number of melanocytes with ↓melanosomes in the melanocytes and keratinocytes
- **Segmental pigmentation disorder** represents a variant that can have a checkerboard pattern of hypopigmentation or hyperpigmentation

### Disorders of hyperpigmentation

#### Melasma

##### Epidemiology

- Young to middle aged women of Asian, Hispanic, African, or Middle Eastern descent

##### Pathogenesis

- Exact pathogenesis unknown, however, **UV irradiation and visible light** may activate hyperfunctional melanocytes to produce more melanin
- Exacerbating factors: **sun exposure, estrogen** (pregnancy, OCPs, and HRT), genetic influences, thyroid dysfunction, and meds (phenytoin and phototoxic drugs)

##### Clinical features

- Common acquired disorder characterized by symmetric, light to dark brown/gray irregular patches on face
  - Three patterns: centrofacial, malar, and mandibular
  - Four types: epidermal, dermal, mixed, and indeterminate
    - Epidermal areas accentuated with **Wood's lamp**, dermal areas are not



**Figure 3-95.** Lichen planus pigmentosus of the face. (From Molinar VE, et al. What's New in Objective Assessment and Treatment of Facial Hyperpigmentation? – Dermatologic Clinics. Elsevier. 2014)

### Histopathology

- ↑melanin in all layers of the epidermis, ↑melanophages, and nl/↑epidermal melanocytes

### Treatment

- Broad-spectrum sun protection/avoidance
- Cosmetic camouflage
- Epidermal component of melasma can be treated with hydroquinone, tretinoin, steroids, and resurfacing

## Lichen planus pigmentosus

- Variant of lichen planus in young to middle aged adults with skin types III-V
- Irregular oval, brown to gray-brown macules and patches in sun exposed or intertriginous areas (Fig. 3-95)
  - Typically symmetric; may have reticulated or follicular pattern
- On histology, mild perivascular or band-like infiltrate in upper dermis, dermal melanophages, and basal cell degeneration

## Linear and whorled nevoid hypermelanosis

- Heterogeneous, sporadic mosaic skin condition in which a clone of skin cells leads to ↑pigment production
- Hyperpigmented macular Blaschkoid whorls and streaks typically occurring before 1 year of age (Fig. 3-96)
- +/- associated systemic findings: neurologic, musculoskeletal, or cardiac
  - Persists indefinitely; no effective treatment

## Prurigo pigmentosa

- Young adult F > M; Japanese especially
- Pruritic erythematous papules and papulovesicles on back/neck/chest, which develop rapidly and involute in



**Figure 3-96.** Linear or circular arrangement of pigmented macules along the lines of Blaschko. (From Ilgen E, et al. Linear and whorled nevoid hypermelanosis: Dermatoscopic features. J Amer Acad Dermatol. Elsevier. 2008.)

<1 week leaving residual reticulated macular hyperpigmentation

- Treatment: mino/doxycycline, dapsone

## Familial progressive hyperpigmentation

- AD; mutation of KIT ligand gene (*KITLG*)
- Begins in infancy and hyperpigmentation increases in surface area with age
- Diffuse hyperpigmented patches involving palms, soles, lips, and conjunctiva

## Endocrinopathies

- Addison's disease, Cushing's syndrome, acromegaly, and hyperthyroidism can all affect levels of ACTH and MSH, which can lead to generalized ↑pigmentation.

## Pigmentary demarcation lines (AKA Futch's lines, Voight lines, Ito's lines)

- Lines of demarcation between dorsal and ventral skin surfaces in which the dorsal side tends to be more hyperpigmented
- Often seen on anterolateral upper extremity and posteromedial thigh
- More apparent in darker-skinned individuals

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# 4

## Pediatric Dermatology

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### 4.1 NEONATAL DERMATOLOGY

Newborn injuries may develop *in utero* or in the postpartum period, but most are sustained during birth (Table 4-1).

Transient skin lesions of the newborn are benign and generally do not require any active treatment, as they are usually self-limited (Table 4-2).

Non-vascular birthmarks may be present at birth or during early childhood. Some are rarely associated with syndromes of systemic involvement, usually ocular, neurologic, and/or skeletal (Table 4-3).

Congenital malformations are present at birth, but may not become apparent until later in life. The majority of these are rare developmental abnormalities. Those on the face may herald abnormal neuroectodermal development, especially those in the midline. Common locations for congenital cysts and developmental remnants are detailed in Table 4-4. Congenital infections are discussed in Table 4-5.

*Text continued on p. 222*



**Figure 4-1.** Subcutaneous fat necrosis. (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)

Table 4-1. Newborn Injuries

Diagnosis	Epidemiology and Pathogenesis	Clinical Features	Histology and Laboratory Testing	Treatment	Prognosis/Clinical Course
Caput succedaneum	Occurs after prolonged labor Pressure during labor leads to extravasation of blood/serum <b>above the periosteum</b>	Diffuse swelling of the scalp; <b>crosses suture lines</b> ; +/- ecchymoses		None	Presents at birth; resolves over several days
Cephalohematoma	Occurs after prolonged labor Rupture of emissary/diploic veins during labor, resulting in <b>subperiosteal</b> hemorrhage	Unilateral swelling most commonly over parietal bones; <b>does not cross suture lines</b> ; no bruising	CBC Bilirubin if severe	None	Presents hours to days after birth; resolves over weeks
Subgaleal hematoma	Occurs after traumatic/instrumented delivery Emissary veins rupture during traumatic delivery; bleeding into <b>subgaleal</b> space	Large area of dependent edema; +/- fluid waves; crosses suture lines and can extend from nape of neck to brow line; can lead to <b>anemia, DIC, and shock</b>	CBC; coagulation studies if severe	Close inpatient monitoring; fluids and blood products as indicated	Presents shortly after birth
Halo scalp ring	Occurs after prolonged labor Localized injury/soft tissue hypoxia during birth	Annular band of alopecia 1–4 cm wide over vertex, and scalp; associated caput; +/- necrosis and scarring		Wound care if necrotic; surgical excision for large areas; developmental monitoring	Presents shortly after birth; hair regrows in mild cases
Subcutaneous fat necrosis	Seen in <b>healthy</b> full-term and post term neonates, and neonates receiving therapeutic hypothermia Hypoxic injury to fat; caused by trauma, perinatal complications	One to several indurated violaceous/red plaques/nodules; favors fat-rich anatomic sites, such as <b>back, cheeks, buttocks, and thighs</b> (Fig. 4-1)	Necrosis and crystallization of <b>fat with needle-shaped clefts</b> , granulomatous inflammatory infiltrate <b>Screen for hypercalcemia for 6 months</b>	Supportive care; avoid vitamin D supplementation; management of hypercalcemia as indicated	Presents in <b>first few weeks of life</b> ; resolves over weeks to months; may leave scarring
Sclerema neonatorum	Occurs in <b>debilitated preterm</b> and term infants, now seen only in developing countries Impaired neonatal lipoenzymes and abundance of saturated fatty acids leads to fat solidification and sclerema	Sudden appearance of <b>diffuse hardening of skin</b> in first few weeks of life; spares palms, soles, and genitals	Lipid crystals form rosettes of fine needle-like clefts but <b>lacks granulomatous inflammation</b> (vs. SQ fat necrosis of newborn)	Intensive supportive care; systemic steroids controversial	<b>Most succumb to sepsis and shock</b> ; process can reverse if underlying conditions are treated

**Table 4-2.** Transient Skin Lesions of the Newborn

Diagnosis	Epidemiology and Pathogenesis	Clinical Features	Histology and Laboratory Testing	Prognosis/Clinical Course
Erythema toxicum neonatorum	<b>Full-term</b> infants, >2500 g	Erythematous macules, papules, pustules, and wheals; may occur anywhere except palms and soles	Subcorneal and intrafollicular eosinophilic pustules Wright's stain of pustule fluid: <b>eosinophils</b>	Usually presents at <b>24–48 hours</b> , but can be seen from birth to 2 weeks Self-limited and resolves over several weeks
Transient neonatal pustular melanosis	Term infants; more common in <b>blacks</b>	Three stages: <b>pustules</b> without underlying erythema; <b>collarettes of scale</b> ; <b>hyperpigmented macules</b> . Lesions may be clustered together; may be seen anywhere, but most often forehead, ears, back, fingers, and toes (Fig. 4-2)	Subcorneal pustules with neutrophils, fibrin, and rarely eosinophils Wright's stain of pusule fluid: <b>neutrophils</b>	<b>Presents at birth, or shortly thereafter</b> , but collarettes or hyperpigmentation are occasionally noted at a few days to weeks of age; self-limited and resolves over several weeks
Congenital milia	16%–50% of newborns Tiny inclusion cysts in epidermis arising from infundibula of vellus hairs	Minute, white, and smooth papules typically seen on face; few to several dozen Of note, orofacial digital syndrome presents with numerous and persistent milia		Resolve over several months without treatment
Bohn's nodules/ Epstein pearls	Microkeratocysts of the mouth that form along embryonic lines of fusion	1–2 mm gray-white, smooth papules along the <b>palatal raphe (Epstein)</b> or the <b>alveolar ridge (Bohn)</b>		Most resolve spontaneously by 5 months
Eosinophilic pustulosis/ folliculitis	Mean age of onset 6 months; male > female	Pustules and erythema Mainly involves scalp and face; occasionally trunk and extremities	Dense perifollicular mixed infiltrate with eosinophils CBC (eosinophilia)	Presents at birth or days to weeks of age May be pruritic Waxing and waning course over months with recurrent crops of pustules that eventually remit
Miliaria crystallina	Intracorneal obstruction of eccrine duct; typically a history of fever or overheating	Fragile, <b>clear-colored vesicles</b> without underlying erythema; forehead, upper trunk, and arms most commonly		May be seen in neonates and infants Self-limited
Miliaria rubra	Deeper intraepidermal obstruction of eccrine duct with inflammation; sometimes a history of overwarming, fever, or use of occlusive dressing or garment	<b>Erythematous papules</b> with superimposed pustules typically concentrated in one or two areas; favors <b>intertriginous/occluded sites</b> (neck, groin and axillae) most commonly affected areas	Dermal inflammation around occluded eccrine ducts	May be seen in neonates and infants Self-limited



**Table 4-3.** Nonvascular Birthmarks\*\*\*

Diagnosis	Epidemiology and Pathogenesis	Clinical Features	Histology	Treatment and Prognosis/Clinical Course	Additional Boards Fodder
Connective tissue nevus (CTN)	Hamartoma comprised of excessive deposition of one or more components of dermal connective tissue (collagen, elastin, or glycosaminoglycans) Can occur sporadically or as a part of one of several AD familial genodermatoses	Asymptomatic, firm, and <b>skin-colored to yellowish nodules/plaques</b> on trunk/limbs; can be solitary or multiple; can have cobblestone, leather grain, or p'eu d'orange texture; present at birth or become evident in childhood/adolescence	Dermis shows <b>excessive collagen or elastic tissue</b> , or both Findings may be subtle, so need to take biopsy of adjacent normal uninvolved skin for comparison	No treatment needed; can be excised if cosmetically indicated Grows with somatic growth, stable over time; no malignant potential	<u>Manifestations of CTN in genodermatoses</u> : "Shagreen patch" or collagenoma (presents later childhood) in <b>tuberous sclerosis</b> Multiple elastic tissue nevi with osteopoikilosis in <b>Buschke-Ollendorff syndrome</b> Familial cutaneous collagenoma: hypogonadism and cardiomyopathy Cerebriform collagenoma on sole of foot may be isolated or a component of <b>Proteus syndrome</b>
Congenital smooth muscle hamartoma	Slight male predominance Hamartoma of reticular dermis comprised of dense arrector pili muscle	<b>Hyperpigmented plaque</b> or patch with overlying hypertrichosis, sometimes perifollicular papules; most commonly on <b>lower back/lumbosacral area</b> , but also proximal extremities; typically single lesion, but (rarely) can be multiple; evident at birth or shortly thereafter	Many well-defined and variably oriented <b>bundles of smooth muscle</b> within reticular dermis	No treatment needed; can be excised if cosmetically indicated No malignant potential	<b>Becker's nevus</b> may have significant histological overlap with congenital smooth muscle hamartoma (both have increased bundles of smooth muscle in dermis and epidermal hyperpigmentation), but Becker's nevus tends to arise in peripubertal period, favors upper trunk and arms, and may be a/w hypoplasia of underlying structures (esp. breast hypoplasia)
Nevus simplex ("salmon patch")	<b>Very common</b> (up to 50% of all newborns), benign, transient vascular ectasia of capillary bed	<b>Ill-defined, pink</b> to light-red, blanchable macules and patches on glabella (" <b>angel's kiss</b> "), eyelids, and occiput (" <b>stork's bite</b> "); more rarely on nose, upper lip, and lumbosacral back	Superficial capillaries in upper dermis with normal overlying skin	Treatment not indicated unless lesions persist and cosmetically needed, in which use of pulsed-dye laser may be considered Most <b>resolve over few months to years</b> , but lesions in occipital area often persist	More extensive lesions called "nevus simplex complex"; compared to port wine stains, nevus simplex lesions are far more common (50% vs 1% of newborns), more poorly defined, lighter pink (vs deep red or "wine-colored"), and transient
Dermal melanocytosis (DM)	<b>African American (95%) &gt; Asian (85%) &gt; Latino (65%) &gt; Caucasian (13%)</b> neonates Defect in migration of pigmented neural crest cells that fail to migrate to dermoepidermal junction	<b>Slate blue, gray</b> , or black patches, often several cm in diameter, most commonly over <b>buttocks and sacrum</b> , but can occur anywhere (Fig. 4-3) Subtypes of dermal melanosis at specific sites: <b>nevus of Ota</b> (around eye/cheek and sclera; most common in Asians) and <b>nevus of Ito</b> (shoulder girdle; most common in Asians)	Collections of spindle-shaped melanocytes dispersed in normal, non-sclerotic dermal collagen (vs. sclerotic in blue nevus)	No treatment recommended for most dermal melanocytosis Use of <b>Q-switched lasers</b> (ruby, alexandrite or Nd:YAG) is ToC for nevus of Ota/Ito (90% effective!) <b>Sacral lesions tend to fade/disappear</b> over few years; other sites may persist	Blue color from the <b>Tyndall effect</b> (blue wavelengths reflected back from deep melanin in skin); extensive dermal melanocytosis described in infants with GM1 gangliosidosis, phakomatosis pigmentovascularis

\*\*\*Epidermal nevus, nevus sebaceus, nevus comedonicus, porokeratotic eccrine ostial and dermal duct nevus are discussed in the Neoplastic Dermatology chapter.



**Figure 4-2.** (A) Transient neonatal pustular melanosis first appears as small, superficial pustules without inflammation. (B) Collarettes of scale, typical of the second stage, are occasionally seen at birth without evident pustules or (C) may develop after pustules have ruptured. (D) The final stage is that of small hyperpigmented macules resembling lentils, which gradually fade over weeks to months. (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)



**Figure 4-3.** Dermal melanosis (Mongolian spots) on the back and buttocks. (Courtesy of Dr S. Friedlander.) (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)

**Table 4-4.** Developmental Abnormalities\*\*\*

Diagnosis	Pathogenesis	Clinical Features	Histology and Laboratory Testing	Treatment and Prognosis/ Clinical Course	Additional Boards Fodder
Aplasia cutis congenita/hair collar sign	No single underlying cause; in midline cases, incomplete closure of neural tube; in lateral cases, incomplete closure of embryonic fusion lines	Solitary 0.5–10 cm (rarely multiple) well-demarcated round to stellate areas of <b>localized absence of epidermis, dermis, and sometimes subcutis and calvarium</b> ; presents as an ulcer, erosion, or glistening membrane at birth that resolves leaving an <b>alopecic scar</b> ; most (up to 90%) occur on scalp (near hair whorl), but may be seen on the face, trunk, and extremities; the <b>hair collar sign</b> is a congenital ring of dense, dark, and coarse terminal hair around an area of aplasia cutis or other congenital scalp lesion, suggesting <b>cranial dysraphism</b> (Fig. 4-4)	Epidermis is atrophic; superficial dermis replaced by loose connective tissue with absent adnexal structures; hair collar shows hypertrophic clustered hair follicles Radiologic imaging (MRI) if concern for underlying CNS extension/calvarial defect	No intervention for small lesions Surgical excision if large (>4 cm <sup>2</sup> ) to minimize chance of complications (e.g., hemorrhage, meningitis, and thrombosis) Spontaneously resolves with scarring; if located in midline and associated with a palpable component, there is a higher risk of underlying calvarial/CNS defect	Associated with teratogens ( <b>methimazole</b> ), <b>Adams-Oliver syndrome</b> (aplasia cutis w/cranial defect + congenital heart defects + CMTC + limb abnormalities), <b>Bart syndrome</b> (aplasia cutis + DDEB), omphalocele, gastroschisis, spinal dysraphism, meningocele, trisomy 13, ectodermal dysplasias, focal dermal hypoplasia, amniotic band syndrome, and congenital infections (e.g., VZV, HSV) May widen nasal bone, giving appearance of hyper-telorism
Nasal glioma	Ectopic neuroectoderm	Firm, noncompressible, nontender usually skin-colored (can be blue-red) nodule at <b>root of nose</b> ; can occur in extranasal (60%) or intranasal (30%) locations		Surgical excision Stable over time, no intracranial extension	
Meningocele/encephalocele	Herniation of cranial contents through skull defect; neuroectoderm did not properly separate from surface ectoderm in early gestation	Compressible subcutaneous nodule that <b>transilluminates</b> , typically at occiput; also can occur on dorsal nose, orbits, and forehead	Type of neural tissue present determines encephalocele (meningeal and glial tissue) versus meningocele (meningeal tissue only) <b>Radiologic imaging necessary</b> for surgical planning	Surgical excision Enlarge with increased intracranial pressure (e.g., crying, straining) as a result of connection to CNS	Can be associated with brain malformation, hypertelorism, and facial clefting; presence of hair collar sign, capillary stain, and mass highly suspicious for cranial dysraphism
Accessory tragus	Congenital; faulty development of first branchial arch	Exophytic papule(s), with/without cartilage, occur anywhere from <b>preauricular region to angle of mouth</b> ; single to multiple; can be bilateral	Tiny hair follicles amidst connective tissue, sometimes with cartilaginous core	Careful surgical resection (cartilage can be contiguous with external ear canal)	Typically isolated, but can be associated with other branchial arch syndromes (e.g., oculauriculovertebral or <b>Goldenhar syndrome</b> )

Congenital rests of the neck (wattles)	Remnants of branchial arches; occur along branchial arch fusion lines	Soft fleshy to firm cartilaginous nodules along the cervical neck (anterior border of sternocleidomastoid)	Mature cartilage lobules embedded in cartilage	Surgical excision (may contain cartilage)	
Midline cervical cleft	Congenital midline defect of ventral neck	Small skin tag above a vertically oriented linear atrophic patch; can be small sinus containing ectopic salivary tissue at bottom of atrophic patch		Surgical excision	Can be associated with cleft lip, palate, mandible, chin, tongue, or midline neck hypoplasia
Lip pits	Incomplete closure of furrows on mandibular process	Bilateral indentations on vermilion lower lip; can be unilateral Associated with cleft lip or palate (Van der Woude syndrome)	Fistulous lumen lined by stratified squamous epithelium with scattered mucinous acini Evaluate for cleft lip/palate, if indicated	Surgical repair May be associated with abnormal salivation	
Umbilical granuloma	Incomplete epithelialization after umbilical cord separation	<b>Bright red, friable</b> , broad-based papule; not present at birth	Inflamed vascular granulation tissue	<b>Silver nitrate</b> (caution in large lesions) Resolve over weeks to months	
Developmental anomalies of the umbilicus	Urachal remnant or omphalomesenteric duct fails to regress	Red to pink nodule within umbilicus, sometimes with mass underneath <b>Persistent drainage</b>	Abrupt transition from stratified squamous epithelium to glandular epithelium Consider abdominal U/S; referral to pediatric surgery	Surgical excision Can become infected and irritated	
Amniotic band syndrome	Premature rupture of the amniotic sac and formation of fibrous strands	Circumferential constriction band of the distal extremity; distal lymphedema, ischemia, and <b>amputation</b> ; early rupture can lead to other extracutaneous malformations		Surgical correction Constriction can lead to ischemia and amputation	
Dermoid cyst	Faulty development along embryonic fusion lines	Firm, nontender, skin to blue-colored subcutaneous nodules most commonly seen on the <b>upper lateral forehead</b> , <b>near the eyebrow</b> , overlying the anterior fontanelle, or at the junctional of sagittal and coronal scalp sutures, but can be seen anywhere on the face, scalp, or spinal axis. May adhere to the underlying periosteum.	Imaging is recommended (MRI most often) for those present in the midline. Histology shows cysts lined by stratified squamous epithelium, and may contain hair follicles, sebaceous glands, and sweat glands.	Surgical excision is the treatment of choice. Lesions usually do not recur.	

\*\*\*Branchial cleft cysts, bronchogenic cysts, median raphe cysts, and thyroglossal duct cysts are discussed in the Neoplastic Dermatology chapter.



Table 4-5. Congenital Infections

Diagnosis	Epidemiology/Pathogenesis	Clinical Features	Histology and Laboratory Testing	Treatment Prognosis/ Clinical Course	Additional Boards Fodder
Congenital rubella	Maternal infection (in <b>first 12 weeks of gestation leads to most severe disease</b> ), leads to infection of fetal cells and defective organogenesis	Skin: intradermal <b>extramedullary hematopoiesis</b> (EMH), which appears as soft spongy 2–20 mm erythematous to violaceous papules (“ <b>blueberry muffin baby</b> ”); hemorrhage, petechiae may be seen Other: small for gestational age, microcephaly, <b>deafness (most common symptom)</b> , <b>cataracts</b> , congenital heart disease, chorioretinitis, retinopathy, patent ductus arteriosus, intracranial calcification, and hepatosplenomegaly	EMH; erythroid (nucleated RBCs) precursors, immature granulocytes, and megakaryocytes Viral culture of nasopharynx; serology less sensitive, but can do acute (cord blood) and convalescent (4–6 months) titers	No treatment Universal vaccination is designed to prevent congenital infection <b>Manifestations of congenital rubella are lifelong</b> , but can present later in childhood	
Congenital toxoplasmosis	Consumption of undercooked meats and exposure to <b>cat feces</b>	Congenital: chorioretinitis, hydrocephalus, <b>intracranial calcifications</b> +/- petechial rash, extramedullary hematopoiesis (EMH; “blueberry muffin baby”) Postnatal: majority are asymptomatic; very variable presentation	EMH Serology PCR of amniotic fluid Histology of lymph nodes	Pyrimethamine, sulfadiazine, folinic acid $\times$ 1 year Prognosis improves with therapy, but consequences can be severe	
Congenital CMV	<b>Most common congenital infection and most common cause of EMH</b> Three methods of infection: 1. Reactivation of latent maternal disease $\rightarrow$ no stigmata of disease 2. Primary maternal infection during pregnancy (earlier, more severe) 3. Postnatal exposure during delivery or while breastfeeding	<b>“Blueberry muffin” spots</b> (EMH), petechiae, intrauterine growth restriction, microcephaly, cerebral palsy, chorioretinitis, hepatosplenomegaly, and pneumonitis <b>Most common infectious cause of congenital deafness and mental retardation!</b>	EMH Culture: urine and saliva PCR: plasma Serology (rarely used in the neonate): rising IgG titer, IgM not sensitive in neonate	<b>IV gancyclovir</b> Oral valgancyclovir (limited data in newborns) Congenital CMV cannot be cured, only suppressed	
Congenital syphilis	Presents at birth or first few days of life; lack of prenatal care in ~30% of cases; mothers with primary or secondary syphilis; incidence increasing in some areas of the United States Invasion of placenta, bloodstream and organs by <i>T. Pallidum</i> ; adhere to endothelium and cause vasculitis	Early (<2 years of age): condyloma lata, bullae, or erosions favoring hands, feet, and periorificial areas; scaling, erythema, and <b>secondary syphilis-like papulosquamous lesions</b> , and mucous patches; hepatosplenomegaly, <b>snuffles</b> , jaundice, <b>Parrot pseudoparalysis</b> (due to painful epiphysitis), anemia, and edema Late (>2 years of age): interstitial keratitis, nerve deafness, <b>saber shins</b> , gummas of bone, frontal bossing, <b>Higoumenakis sign</b> (enlargement of medial third of clavicle), <b>mulberry molars</b> , <b>Hutchinson teeth</b> , <b>saddle nose</b> , perioral <b>rhagades/Parrot lines</b> and Clutton joints (painless, symmetric swelling of <b>knees</b> ), tabes dorsalis	Swelling and proliferation of endothelial cells; perivascular infiltrate of plasma and lymphoid cells Dark field exam of skin; DFA; syphilis serologies - VDRL, RPR titer in infant 4x mother's titer, but can have false negatives if disease acquired late in pregnancy; IgM FTA-Abs most specific; skin biopsy	<b>Penicillin</b> (route and course according to clinical features and per CDC and AAP guidelines) Depends on severity at presentation; prognosis for promptly treated syphilis is excellent	False positive nontreponemal tests (VDRL and RPR) in: infectious diseases, malignancies, and connective tissue diseases FTA-Abs, MHA-TP false positive with other spirochetes and Lyme disease

<p>Congenital varicella</p>	<p><u>Fetal</u>: infection in <b>first 20 weeks gestation</b>  <u>Neonatal</u>: maternal primary varicella infection <b>7 days before to 2 days after delivery</b></p>	<p><u>Fetal</u> (presents at birth): stellate deep scars; limb paresis; hypoplasia; chorioretinitis; and low birth weight; mental retardation; microphthalmia, cataracts; nystagmus; and hydrocephalus  <u>Neonatal</u> (presents at 0–14 days): vesicles on erythematous base; lesions usually in same stage of development; generalized distribution, often much more widespread than outside newborn period</p>	<p>Neonatal: intraepidermal blisters associated with intracellular edema and multinucleate epithelial cells with inclusion bodies  Tzanck, FA, viral culture, and serology unreliable; prenatal imaging (US, MRI); virus usually not isolated from fetal varicella syndrome cases</p>	<p><b>VZIG</b>  Acyclovir  Fetal: varies based on extracutaneous manifestations  Neonatal: infection at &lt;5 days has a <b>fatality rate of up to 30%</b>; infection after 5 days has a benign course</p>	<p>Zoster in first year of life without history of primary varicella infection is seen with exposure to varicella <i>in utero</i>; infants &lt;1 year of age are more likely to develop secondary streptococcal infection</p>
<p>Congenital (intrauterine) herpes simplex</p>	<p>Birth, first few days of life  Via ascending infection (secondary maternal infection) or viremia from primary maternal infection</p>	<p>Vesicles, pustules, widespread erosions, congenital scars, and areas of aplasia cutis  Any site may be involved, but scalp often affected with aplasia cutis-like areas; signs of TORCH infections, e.g., low birthweight; microcephaly, and chorioretinitis; 50%–75% mortality if untreated</p>	<p>Tzanck; fluorescent antibody or immunoperoxidase slide test, PCR, and viral culture</p>	<p>IV acyclovir</p>	
<p>Neonatal herpes simplex</p>	<p>Presents at 5–14 days  Infection during birth or perinatal period</p>	<p>Skin, eyes, and mouth (SEM); disseminated infection; <b>CNS infection (40% have neurologic sequelae)</b>  Skin: vesicles, pustules, crusts, and erosions (predilection for scalp and torso); may involve mucosa (Fig. 4-5)  Signs of sepsis: irritability and lethargy</p>	<p>Intraepidermal blisters associated with intracellular edema and multinucleate giant cells with inclusion bodies  Tzanck; DFA or immunoperoxidase slide test, PCR, and viral culture</p>	<p>IV acyclovir  Usually 5–14 days</p>	
<p>Congenital candidiasis/neonatal candidiasis</p>	<p>Risk factors: prematurity, foreign body in cervix/uterus, and maternal vaginal candida colonization  Ascending intrauterine chorioamnionitis</p>	<p>Presents at birth or first few days to weeks of life with erythema, <b>small monomorphous papules, and pustules</b> (Fig. 4-6)  In extremely premature infants presents as a burn-like dermatitis with scaling  Favors upper torso, palms, and soles  Systemic infection is rare in healthy term infants</p>	<p>Skin biopsy may be helpful if KOH negative and manifests subcorneal pustule with neutrophils; PAS will highlight yeast forms  KOH: hyphae and budding yeast</p>	<p>If localized, can be treated with topical imidazole or nystatin; if extensive, or if the infant is ill, preterm, or very low birth weight, use of systemic antifungal is indicated  Limited disease in healthy term infants resolves quickly with topical treatment  Premature infants may have significant associated morbidity</p>	



**Figure 4-4.** Membranous aplasia cutis with a subtle hair-collar sign. (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)



**Figure 4-5.** Neonatal herpes simplex virus. Multiple vesicles and crusted papules on an erythematous base in the periumbilical area and left flank. (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)



**Figure 4-6.** Congenital candidiasis. Diffuse erythematous and pustular eruption. (From Eichenfield LF, et al. *Neonatal and Infant Dermatology*, 3rd Ed. Elsevier. 2015)

## 4.2 VIRAL EXANTHEMS AND SELECT INFECTIOUS DISORDERS OF CHILDHOOD

### Rubeola (measles, “First Disease”)

- Outbreaks occur in areas where immunization rates are low
- Caused by the measles virus (RNA virus; paramyxovirus family)
- Transmitted via **respiratory droplets**
- Infection begins in the nasopharynx or conjunctiva → subsequent spread to lymph nodes/blood (viremia)
- 1- to 2-week incubation period → fever and prodrome of cough/coryza/conjunctivitis (3 Cs)
  - Enanthem: **Koplik spots** (gray/white papules on buccal mucosa; resolve before exanthem)
  - Exanthem: morbilliform eruption (maculopapular) that **starts on frontal hairline and postauricular areas**, and subsequently spreads in a **cephalocaudal** fashion
- Possible complications: upper or lower respiratory tract infection, otitis media, gastrointestinal (GI) symptoms, **encephalitis**, myocarditis, and **SSPE (subacute sclerosing panencephalitis; occurs years after infection)**
- Measles specific serologies can be performed for diagnosis:
  - IgM may initially be negative for 3 days after rash onset
  - Expected four-fold increase in IgG with infection
  - PCR from nasopharyngeal swab or urine is another diagnostic option
- **Vitamin A** supplementation recommended for pediatric patients in communities with vitamin A deficiency, those aged 6 months to 2 years of age hospitalized with the disease, and those >6 months with risk factors
- Measles vaccine may be helpful if given within 3 days of exposure, and immunoglobulin may be given within 6 days of exposure
- Prevention of disease via a two-dose immunization series (measles/mumps/rubella); **first dose at age 12–15 months and second dose at age 4–6 years**

### Rubella (German measles, “3-day measles,” or “Third Disease”)

- Caused by rubella virus (RNA virus; togaviridae family)
- Transmitted via respiratory droplets (like measles); nicknamed “3-day measles” because **resembles measles in many ways, but has shorter and milder course**; most important concern is to avoid infection during pregnancy (a/w **TORCH syndrome**)
- Infection begins in nasopharynx, then spreads to the lymph nodes; viremia subsequently develops
  - Prodrome: fever, headache, and URI symptoms
  - Exanthem: **morbilliform eruption that starts on head/neck** (like measles) and spreads in a **cephalocaudal** fashion
  - Enanthem: **Forchheimer’s spots** (palatal petechiae)



- Lymphadenopathy typically generalized/painful w/ involvement of **suboccipital/postauricular/anterior and posterior cervical lymph nodes**
- Complications (generally mild): arthritis and arthralgias (~50% of females), hepatitis, myocarditis, pericarditis, hemolytic anemia, thrombocytopenia, and encephalitis
- Diagnosis: (+) Rubella-specific IgM or four-fold increase in IgG over 1 to 2 weeks duration; PCR of nasopharyngeal sample
- Treatment is supportive; administration of immunoglobulin may be considered in exposed pregnant and unvaccinated women

### Erythema infectiosum (“Fifth Disease,” “Slapped cheek disease”)

- Caused by **parvovirus B19** (single stranded DNA virus)
- Transmission by respiratory secretions, blood, and through placenta to fetus of affected mother
  - Infection begins in respiratory tract, followed by viremia (viremia resolves w/ IgM development)
  - IgG development coincides with development of skin eruption and arthritis
  - Parvovirus B19 is tropic to bone marrow and replicates in erythroid precursors (binds to globoside – blood group P antigen); thus, during viremia, **transient decrease in hemoglobin**
- Prodromal symptoms during viremia consisting of fever, myalgias, and headache
- Exanthem develops 1 to 1.5 weeks later
  - **Not contagious once eruption develops**
  - **Slapped cheeks:** erythema of cheeks, sparing central face
    - Facial rash may be absent in adults with infection
  - Subsequent maculopapular eruption with “**lacy, reticulated**” pattern, favoring **extremities** (Fig. 4-7)
    - Fluctuates in intensity over several weeks
- **Arthritis with small joint predominance** may occur
  - More common in **adults** (females > males), rare in children (~10%)
  - May be present without skin findings
  - Those with arthritis are not infectious
- Relative anemia, which is asymptomatic in healthy individuals
  - **Aplastic crises and pancytopenia** may develop in those with predisposing conditions (e.g., **sickle cell anemia** and other hemoglobinopathies)
- Fetal infection
  - Highest risk if acquired before 20 weeks gestation
  - Fetal loss rate highest in second trimester
  - Possible fetal effects: anemia, high-output congestive heart failure, **hydrops fetalis**, and intrauterine fetal demise

### Popular purpuric gloves and socks syndrome

- **Young adult predominance**; due to **parvovirus B19 infection**; most common in spring
- Symmetric edema and erythema of palms/soles, may extend to dorsal surface
- Associated **petechiae and purpura with sharp demarcation at the wrists and ankles**



**Figure 4-7.** Lacy eruption on extensor arm of child with parvovirus B19 infection. (Weston WL, Lane AT, Morelli JG. Color Textbook of Pediatric Dermatology, 4th ed. 2007)

- Resolution over 1 to 2 weeks without treatment
- Patients are viremic at time of skin eruption, therefore, unlike erythema infectiosum, patients are considered infectious when rash is present
- IgM (+) up to 4 months post-infection; IgG (+) after 1 week and persists for life
- Most infections resolve without sequelae

### Exanthem subitum (roseola infantum, “Sixth Disease”)

- 6–24 months of age; occurring most commonly in spring
- Infection with **HHV-6** (HHV-7 less likely), a DNA virus
  - Two variants: HHV-6A (seen in HIV) and HHV-6B (cause of exanthema subitum)
  - Transmitted by oral secretions
- Incubation period of 1 to 2 weeks → **high fever** (>40°C) for up to 5 days (+/- URI symptoms and lymphadenopathy)
  - **Common cause of febrile seizures**
- **Fever resolves as the exanthem begins**
  - Exanthem: generalized but subtle maculopapular eruption, truncal predominance; typically resolves within 2–3 days
  - Enanthem: **Nagayama’s spots**, which are red macules on soft palate and uvula
- **Benign course**; resolves without complications, even in pregnant women; even patients who develop febrile seizures are unlikely to suffer future seizures
- Remains latent in CD4+ T cells, which results in possibility of reactivation
  - Implicated pathogenic factor in DRESS





**Figure 4-8.** Hand-foot-and-mouth disease. (From James WD, Berger T, Elston D, et al. *Andrews' Diseases of the Skin: Clinical Dermatology*, 12th Ed. Elsevier. 2015)

### Hand-foot-and-mouth disease

- Summer/fall predominance, most common in children up to 10yo
- Infection caused by *Coxsackie A16 virus* (> *Coxsackie A6* and *Enterovirus 71*)
- Transmitted by **fecal-oral and respiratory routes** → infection of pharyngeal or GI tract, followed by lymphoid involvement, subsequent viremia, and involvement of end organs, including skin
- Incubation period of 3–6 days → prodrome (fever and malaise) → onset of cutaneous eruption
  - **Vesicular eruption** most commonly involving palms/soles/buttocks/oral cavity
  - Erythematous macules and oval, deep-seated erythematous vesicles and bullae with **gray center** (Fig. 4-8)
  - Erosive lesions can be found in the oral cavity (palate/uvula/tongue/buccal mucosa)
- Boards factoid: *Coxsackie A6* has recently been shown to cause more widespread and severe vesiculobullous eruptions and is a/w atypical HFMD presentations, including **eczema coxsackium** (in atopic patients), **Gianotti-Crosti-like eruptions**, purpuric eruptions, and **onychomadesis** (nail matrix arrest at time of acute infection)

### Gianotti-Crosti syndrome (papular acrodermatitis of childhood)

- Peak age = 1–6 years of age (90% are younger than 4yo)
- Exanthem arising in setting of viral trigger; may also be seen after vaccination
- #1 cause in United States: EBV



**Figure 4-9.** Gianotti-Crosti syndrome. Grouped red papules on leg in child with EBV infection. (From Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology*, 4th ed. Elsevier. 2007)

- #1 cause worldwide: **hepatitis B**
- **Symmetric monomorphic skin-colored to erythematous papular eruption** with predilection for **face (esp. cheeks), extremities, and buttocks** (Fig. 4-9); relative sparing of chest, back and abdomen
- Spontaneous resolution expected within 1–2 months

### Unilateral laterothoracic exanthem (asymmetric periflexural exanthem of childhood)

- Average age = 1–5 years of age; female predominance; usually in spring
- Thought to be 2° to virus, but exact cause unknown
- May have preceding prodromal symptoms of URI or GI illness
- **Unilateral** erythematous macules and papules with flexural predominance, classically beginning in axilla and lateral trunk; **“Statue of Liberty sign”** (a Boards clue) = picture of young child with one arm raised to the sky to show rash on axilla and lateral trunk
- Centrifugal spread to contralateral side may occur, but rash usually maintains unilateral predominance
- Resolves spontaneously after 3 to 6 weeks

### Chronic mucocutaneous candidiasis

- Often autosomal recessive (AR)
- CMC is a heterogeneous group of disorders marked by chronic and recurrent infections of the skin/hair/nails/mucosa with *C. albicans* (e.g., thrush, perleche, chronic paronychia, diaper dermatitis/intertrigo, and dental enamel hypoplasia)
  - APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome): AR disease; CMC and other clinical features as a result of a mutation in the *AIRE* gene
    - *AIRE* (*autoimmune regulator*) mutation results in failure of T-cell tolerance with resultant autoimmunity

- **Additional features seen in APECED**
  - ◆ Endocrinopathies:
    - ➔ **Hypoparathyroidism**, hypoadrenocorticism, hypogonadism, thyroid disease, diabetes, and hypopituitarism
  - ◆ Autoimmune antibodies
  - ◆ Cutaneous autoimmune conditions: **alopecia areata and vitiligo**
  - ◆ Malabsorption
  - ◆ **Pernicious anemia**
  - ◆ Hepatitis
- Additional CMC syndromes are seen in association with mutations in signal transducers and activators of transcription 1 (*STAT-1*), **interleukin-17F (*IL-17F*)**, caspase recruitment domain-containing protein 9 (*CARD9*), and C-type lectin domain family 7 member A (*CLEC7a*, *dectin*)

## 4.3 INHERITED PIGMENTARY DISORDERS

### Hypo-/depigmentation

#### Oculocutaneous albinism (OCA)

- Group of AR disorders involving abnormal melanin and melanosome biosynthesis and transport within melanocytes of skin, hair follicles, and eyes
  - There are four types (OCA 1–4), classified based on the affected gene ([Table 4-6](#))
  - **OCA type 2 is the most common type**, followed by OCA type 1
- Variable pigmentary dilution of the skin, hair, and eyes
  - Many affected patients (**except classic OCA1a**) develop pigmented melanocytic nevi/lentigenes/ephelides

- **Photophobia, nystagmus**, and reduced **visual acuity** of variable severity
- On histology, ↓melanin content w/ normal # of melanocytes
- ↑ risk BCC, SCC (**most common type of skin cancer** in these patients), and melanoma (worse in OCA1)
- Boards Factoid: OCA2-like hypopigmentation is seen in 1% of patients with **Prader-Willi syndrome** and **Angelman syndrome**, which are caused by deletions on chromosome 15q (which includes the *OCA2* gene), if a second mutation is present in the remaining *OCA2* gene

### Silvery hair syndromes

- Includes Chediak-Higashi syndrome (CHS), Griscelli syndrome (GS), and Elejalde syndrome
- All are AR
- Characterized by impaired synthesis, storage, and/or transport of melanosomes and in the case of CHS, other intercellular proteins
- All have **pigmentary dilution** of the skin and hair w/ variable **immunologic** and **neurologic** features
  - Under light microscopy, giant granules or melanosomes may be seen in the hair shaft and keratinocytes
  - Skin biopsy demonstrates hyperpigmented oval melanocytes and poorly pigmented adjacent keratinocytes
- **GS1**: severe **neurologic impairment** developing during early childhood
- **GS2**: combined T- and B-cell **immunodeficiency** → numerous infections and hemophagocytic syndrome
- **GS3**: **least severe GS subtype, primarily cutaneous findings**
- **CHS**: severe multisystem disease that presents in infancy with silvery hair, oculocutaneous albinism, immunodeficiency, bleeding diathesis, and neurologic

**Table 4-6.** Oculocutaneous Albinism

Type	Mutation (all are AR)	Phenotype	Comments
OCA1a	<i>TYR</i> ( <b>absent</b> )	Tyrosinase negative	Generalized and <b>near-complete lack of pigmentation</b> at birth – white hair and skin (hair becomes light yellow over time) <b>Nevi are amelanotic/pink</b> Gray-blue irides <b>Markedly reduced visual acuity</b> , severe photosensitivity, markedly increased risk of <b>SCC</b>
OCA1b	<i>TYR</i> ( <b>decreased</b> to 5%–10% of normal level)	<b>“Yellow mutant albinism;”</b> minimal pigment	No pigmentation of skin/hair at birth → over time, develop some pigmentation Can have amelanotic or pigmented nevi Milder ocular complications compared to OCA1a <b>Temperature sensitive variant (OCA1b TS)</b> : tyrosinase functions at low temperatures, leading to hair pigmentation at cooler anatomic sites (mainly extremities) and white hairs in warmer sites (trunk, intertriginous zones)
OCA 2	<i>OCA2</i> (previously called <b>P gene</b> ; pink-eyed dilution)	Tyrosinase positive	<b>Most common OCA</b> , usually seen in <b>Africans</b> Pigmentary dilution variable, but develop pigmented nevi/lentigenes over time <b>Light brown hair</b> and gray/tan irides
OCA 3	<b><i>TYRP1</i></b>	<b>“Rufous”</b>	Very rare; most commonly occurs in Africa and New Guinea Reddish-bronze skin and red hair color Blue-brown irides
OCA 4	Solute carrier family 45 member 2 ( <i>SLC45A2</i> , formerly <i>MATP</i> )	Resembles OCA2	Exceedingly rare except in <b>Japan</b> (where it accounts for 25% of OCA) Variable clinical presentation ranging from white skin/hair to mild pigmentation of skin/yellow-brown hair; distinguish from OCA2 via molecular studies

degeneration; **death typically occurs by age 10** as a result of the lymphoproliferative **accelerated phase**/hemophagocytic syndrome → pancytopenia and lymphocytic infiltration of liver/spleen/lymph nodes

- Severe neurologic degeneration over time
- On peripheral blood smear, **characteristic giant granules** within cytoplasm of neutrophils, eosinophils, platelets, melanocytes and granulocytes; on bone marrow smear, giant inclusion bodies within leukocyte precursors in CHS
- **Elejalde syndrome**: pigmentary features of Griscelli syndrome + **severe neurologic dysfunction** without immunodeficiency (may represent a variant of GS1)

## Hermansky-Pudlak syndrome

- AR disorder with oculocutaneous albinism, **bleeding diathesis** (due to platelet storage

pool defect), and lysosomal accumulation of **ceroid lipofuscin**

- Disorder of biogenesis of melanosomes and other lysosomal-related organelles, such as platelet dense granules
- More common in **Puerto Ricans** (especially HPS1), Dutch, and Indians of Madras
- Nine associated genes have been described: *HPS1*, *AP3B1*/(*HPS2*), *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*/(*HPS7*), *BLOC1S3*/(*HPS8*), and *BLOC1S6* (*HPS9*)
- Variable pigmentary dilution of the skin, hair with a slight sheen, and pale irides
- Extensive **ecchymoses**, **nosebleeds**, and **menorrhagia**
  - Avoid aspirin and other anti-platelet medications
- Photophobia, strabismus, and nystagmus
- Other complications are **granulomatous colitis**, **progressive pulmonary fibrosis**, **cardiomyopathy**, and **renal failure** as a result of **lysosomal ceroid accumulation**

**Table 4-7.** Features of Chédiak-Higashi Syndrome (CHS) and Griscelli Syndrome (GS)

	CHS	GS1*	GS2	GS3
Gene defect	<b>LYST/CHS1</b>	<b>MYO5A</b>	<b>RAB27A</b>	<b>MLPH</b>
Major sites of gene expression	Melanocytes, platelets, granulocytes, and the CNS	Melanocytes, <b>CNS</b>	Melanocytes, <b>cytotoxic T-cells</b>	Melanocytes
Cellular defect	Impaired biosynthesis and storage of melanosomes, platelet dense granules, and lysosomes within leukocytes	Aberrant translocation of melanosomes along microtubules within melanocytes	Aberrant translocation of melanosomes along microtubules within melanocytes	Aberrant translocation of melanosomes along microtubules within melanocytes
Pigmentary dilution of the skin †	+	+	+	+
Silvery/metallic hair	+	+	+	+
Trichoscopy: clumps of melanin	<b>Small, regularly spaced</b>	<b>Larger, irregularly distributed</b>	+	+
Melanocytes	<b>Giant melanosomes</b>	Lacks giant melanosomes	Lacks giant melanosomes	Lacks giant melanosomes
Neutrophils	<b>Giant granules</b>	Normal-appearing granules	Normal-appearing granules	Normal-appearing granules
Ocular findings	+	–	–	–
Bleeding diathesis	+ <b>Prolonged bleeding time</b> , easy bruising	–	–	–
Recurrent infections	+ Especially skin, lungs, and upper respiratory May have EBV-induced lymphoproliferative syndrome	–	+	–
Other features/comments	<b>Severe gingivitis</b> , <b>periodontitis</b> , and oral mucosal ulceration	<b>Neurologic sequelae</b> are most severe complication	<b>Recurrent infections</b> , <b>immunodeficiency</b> , and <b>accelerated phase/HLH</b> are most prominent features	Generally mild disease; <b>skin-limited</b>
Accelerated phase	+ <b>85%</b>	–	+ Development of hemophagocytic lymphohistiocytosis (HLH)	–
Primary neurologic abnormalities	+ Progressive deterioration	+	– ‡	–

CNS, central nervous system

\***Elejalde syndrome likely represents a variant of GS1** and presents with the pigmentary features of Griscelli syndrome with severe neurologic dysfunction but is not associated with immunodeficiency.

†Often accompanied by hyperpigmentation ± guttate hypopigmented macules in acral and sun-exposed sites.

‡May develop neurologic symptoms secondary to the hemophagocytic syndrome of the accelerated phase.

(Adapted from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Routine histology on non-sun-exposed skin will demonstrate a decreased number of melanosomes and short dendritic processes
- **Absence of dense bodies in platelets** noted on electron microscopy
- Life expectancy = 30–50 years of age; most common cause of death in Puerto Rican patients is **pulmonary fibrosis**
- ↑rates of skin cancer

### Piebaldism

- **Autosomal dominant (AD)** disorder caused by mutations in the *c-KIT* **proto-oncogene** or deletions in the snail family zinc finger 2 (*SNAI2*, *SLUG*)
- **Defective migration of melanoblasts** from neural crest to the ventral midline and failed differentiation of melanoblasts to melanocytes
- **White forelock (poliosis)**; seen in 90% + congenital patterned midline and ventral patches of leukoderma
- Depigmentation is stable and permanent, but otherwise **benign**

### Waardenburg syndrome

- Primarily AD disorder of neural crest development → absence of melanocytes in the skin/hair/eyes/striae vascularis of cochlea
- Features may include a depigmented patch on the forehead w/ **white forelock (poliosis)**, congenital **deafness**, **heterochromia irides**, **synophrys**, **broad nasal root**, and **dystopia canthorum**
- Four clinical types have been described (WS 1–4) (Table 4-8)

## Hyperpigmentation

### McCune-Albright syndrome

- Caused by a **non-inherited postzygotic somatic activating mutation in the *GNAS1* gene**
- **Females >> males**
- **Triad: café au lait macules (CALM), polyostotic fibrous dysplasia, and endocrine dysfunction**
  - Typical CALM are segmental and have jagged borders (“coast of Maine”) (Fig. 4-10)
  - Skeletal lesions (**polyostotic fibrous dysplasia**) usually occur under the CALM, and manifest as gait abnormalities, bone pain, visible skeletal deformity, and recurrent pathological fractures



**Figure 4-10.** Large, segmental café-au-lait macules with a “coast of Maine” border in an infant with McCune-Albright syndrome. (Courtesy Philippe Backeljauw, Cincinnati Children’s Hospital. From Schachner LA, Hansen RC. *Pediatric Dermatology*, 4th ed. Elsevier. 2011.)

**Table 4-8.** Disorders of Melanocyte Development

Human Disease	Inheritance	Gene	Protein	Clinical Features
Piebaldism	AD	<i>c-KIT</i>	KIT tyrosine kinase	Congenital patterned areas of <b>depigmentation</b> , <b>white forelock</b> (90%), and islands of normal and hyperpigmentation within depigmented patches; <b>no internal sequelae</b>
	AD	<i>SNAI2</i>	Snail homolog 2 transcription factor	
WS1	AD	<i>PAX3</i>	Paired box 3 transcription factor	White forelock (20%–60%), synophrys, heterochromia irides, dystopia canthorum (eyes appear widely spaced due to lateral displacement of inner canthi; interpupillary distance is normal), and deafness (20%–40%)
WS2	AD	<i>MITF</i>	Microphthalmia-associated transcription factor	Similar to WS1, but <b>no dystopia canthorum</b> , and <b>deafness</b> is more common
	AR	<i>SNAI2</i>	Snail homolog 2 transcription factor	
WS3 (Klein-Waardenburg syndrome)	AD	<i>PAX3</i> †	Paired box 3 transcription factor	Similar to WS1, plus <b>upper limb abnormalities</b> (hypoplasia, contractures and syndactyly)
WS4	AD, AR	<i>EDNRB</i>	Endothelin B receptor	Similar to WS1, plus <b>Hirschsprung’s disease</b>
	AD, AR	<i>EDN3</i>	Endothelin-3	
	AD	<i>SOX10</i>	SRY-box containing 10	

AD, autosomal dominant; AR, autosomal recessive

†Homozygous *PAX3* mutations have been described in individuals with WS3 whose parents were affected with WS1.

(Adapted from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



- Endocrinologic abnormalities include **precocious puberty**, hyperthyroidism, acromegaly, hypophosphatemic rickets, and infantile Cushing syndrome

### Reticulate acropigmentation of Kitamura

- Rare – majority of patients are **Japanese**
- AD – caused by mutations in *ADAM10* (encodes a disintegrin and metalloproteinase 10)
- Slightly depressed, lentigo-like hyperpigmented macules coalescing into a **reticulated pattern on the dorsal hands and feet**
- Hyperpigmented macules may darken and distribution may expand over time
- Palmoplantar pits and abnormal dermatoglyphics may be noted
- On histology, epidermal atrophy and elongated rete ridges with increased melanin and an increased number of melanocytes

### Dowling-Degos disease (DDD)

- Rare – AD inheritance
- Mutations in **keratin 5 gene** (also a/w epidermolysis bullosa simplex with mottled pigmentation)
- **Onset usually during adulthood** w/ reticulated hyperpigmentation involving **axilla and groin**, may spread to gluteal and inframammary folds, neck, torso, inner thighs
- **Comedone-like lesions** on the back or neck, pitted perioral scars, epidermoid cysts, and hidradenitis suppurativa have also been reported
- On histology, increased pigmentation of basal layer and “antler-like” pattern with finger-like rete ridges
  - Dermal melanophages and mild perivascular lymphohistiocytic infiltrate
  - **Galli-Galli disease**: variant of DDD in which suprabasilar **acantholysis** is noted on histology

### Lentiginoses syndromes (Table 4-9)

#### Hereditary dyschromatoses

Dyschromatoses = both hypo- and hyperpigmentation

### Dyschromatosis symmetrica hereditaria (acropigmentation of Dohi)

- Majority of patients are Japanese or Chinese
- AD – caused by heterozygous mutations in the *ADAR (SRAD) gene* (encodes an RNA-specific adenosine deaminase)
- Presents by 6 years of age with dyschromia and hyperpigmented/hypopigmented macules restricted to sun-exposed skin on the dorsal aspects of the extremities and face

### Dyschromatosis universalis hereditaria

- Most cases are Japanese
- AD/AR – mutations in *ABCB6* (ATP-binding cassette subfamily B, member 6)
- Generalized or torso-predominant, well-demarcated brown macules interspersed with variously sized hypopigmented macules with a mottled appearance
- Nail dystrophy and pterygium
- Reports of associations with short stature, idiopathic torsion dystonia, X-linked ocular albinism, photosensitivity, and neurosensory hearing loss

### Dyskeratosis congenita (Zinsser-Engman-Cole syndrome)

- AD, AR, and x-linked recessive (XLR) (**most common**) forms
- **Males > females** (females may have less severe clinical features)
- Occurs 2° to mutations in the *TERT*, *TERC* (AD inheritance), *DKC1* (XLR inheritance), or *TINF2* genes
  - Involved in **telomere maintenance** – affected patients manifest reduced telomerase activity and abnormally shortened telomeres → chromosomal instability/cellular replication dysfunction
- Clinical features: **bone marrow failure** (up to 90%) + **triad of abnormal skin pigmentation, oral leukoplakia and onychodystrophy**
  - Dyspigmentation: **reticulated, poikilodermatous patches** of the **face/neck/upper torso**
  - Nail abnormalities: **anonychia, pterygium, and longitudinal ridging and splitting**
  - Oral manifestations: **leukoplakia (premalignant)**, dyspigmentation, taurodontism, and erythematous patches
  - Other dermatologic features: palmoplantar hyperkeratosis, hyperhidrosis, and diffuse non-scarring alopecia
  - Other features: blepharitis/conjunctivitis, epiphora, ectropion, progressive periodontal disease, developmental delay, esophageal stricture, pulmonary fibrosis, and hepatic cirrhosis
  - ↑ risk for malignancy (**hematopoietic malignancies** and **squamous cell carcinoma** of the oral mucosa/anus/genitalia/esophagus/skin)
  - Causes of mortality include bone marrow failure, pulmonary fibrosis, and malignancy (3rd to 4th decade)
    - Median age at death = 16 years

### Naegeli-Franceschetti-Jadassohn syndrome (NFJS)/dermatopathia pigmentosa reticularis (DPR)

- Rare – AD inheritance
- Mutations in **keratin 14** (NFJS and DPR are allelic ectodermal dysplasia disorders that share many clinical features)

**Table 4-9.** Lentiginoses Syndromes

Syndrome	Gene/Inheritance	Cutaneous Findings	Extracutaneous Findings
<b>LEOPARD syndrome</b> <b>Lentigines</b> <b>ECG defects</b> <b>Ocular hyper-telorism</b> <b>Pulmonic stenosis</b> <b>Abnormal genitalia</b> <b>Retardation of growth</b> <b>Deafness-sensorineural</b>	Missense mutations in <b><i>PTPN11</i></b> / <b><i>SHP2</i></b> seen in 90% <i>RAF1</i> mutations in 3% <b>AD</b>	Lentigines involving the face, neck, and upper trunk are the most common presenting feature (86%) and develop at 4–5 years of age as pinpoint to 5-mm brown-black macules Café noir spots larger and more pigmented Numerous café-au-lait macules Abnormal dermatoglyphics	Hypertrophic cardiomyopathy in 71% Facial dysmorphism Genital abnormalities—gonadal hypoplasia, cryptorchidism, delayed puberty, and hypospadias Skeletal—mandibular prognathism and short stature Joint hyperextensibility Granular cell myoblastomas
Carney complex <b>NAME:</b> nevi, atrial myxomas, ephelides <b>LAMB:</b> lentigines, atrial myxomas, blue nevi	50% with mutations in <b><i>PRKAR1A</i></b> gene, chromosome 17q22–24 Others with changes at chromosome 2p16 <b>AD</b>	Periorificial lentigines are seen in 77%; fade with time Blue nevi are seen in 43%; fade with time <b>Epithelioid blue nevi</b> (highly specific) Cutaneous myxomas Café au lait macules Skin myxomas involving the eyelids, ear, nipple, breast, and mucosa are seen in 33%	<b>Cardiac myxomas</b> (50%–80%; may embolize) Endocrine neoplasms, especially <b>primary pigmented adrenocortical disease</b> (26%–45%) <b>Sertoli cell tumor seen in 33%</b> Thyroid nodules/carcinoma <b>Psammomatous melanotic schwannoma</b> Breast ductal carcinoma
Peutz-Jeghers syndrome	Serine/threonine kinase <b><i>STK11</i></b> / <b><i>LBK1</i></b> gene, chromosome 19p.13.3 in up to 70% <b>AD</b>	<b>Pigmented macules on lips</b> , buccal mucosa, digits, and other mucosa are seen in 50%–60% by age 20 ( <b>Fig. 4-11</b> ) May fade with time No relationship between severity of pigmentation and polyps	<b>GI polyps, most common in the jejunum and ileum→ can cause intussusception (most common), GI bleeding, anemia, and vomiting</b> 93% develop <b>cancer</b> before age 65: <b>GI most common</b> (small intestine, stomach, esophagus, colon or pancreas), lung, and breast Adenocarcinoma seen in younger patients
Laugier-Hunziker syndrome		Pigmented macules on <b>lips</b> , buccal mucosa, <b>genitals</b> , and other mucosa <b>Melanonychia</b> in ~50%	No increased cancer risk
Cronkhite-Canada syndrome		<b>Lentigines</b> of hands, feet, and buccal mucosa <b>Nail dystrophy</b> <b>Alopecia</b>	Intestinal polyposis
Centrofacial lentiginosis (Touraine's syndrome)	<b>AD</b>	Lentigines in first year of life—especially on nose and cheeks Sacral hypertrichosis	Developmental delay Congenital mitral valve stenosis Seizures Absent middle incisors Skeletal abnormalities Dwarfism Endocrine dysfunction
Bannayan-Riley Ruvalcaba syndrome	<b><i>PTEN</i></b>	Lipomas <b>Penile lentigines</b>	<b>Macrocephaly</b> Vascular anomalies—deep, high flow <b>Developmental delay</b> Intestinal polyps Macroductyly Pseudopapilledema Hashimoto thyroiditis Increased risk of malignancy

- **NFJS:** brown-gray reticulated hyperpigmentation typically localized to the abdomen, develops in early childhood (around age 2), and **improves after puberty**
  - Other findings: palmoplantar keratoderma, adermatoglyphia, onychodystrophy, hypohidrosis, and **dental anomalies** (not seen in DPR) including early loss of teeth
- **DPR: diffuse non-scarring alopecia** (not seen in NFJS), onychodystrophy, adermatoglyphia, and diffuse, **persistent reticulated hyperpigmentation** of the torso and proximal extremities
  - **Pigmentary changes fade in NFJS, but persist in DPR;** only DPR has alopecia; only NFJS has teeth abnormalities



**Figure 4-11.** Peutz-Jeghers. Note lentiginos on mother's fingers also. (Personal collection, Dr. Megha Tollefson)

## 4.4 EPIDERMOLYSIS BULLOSA (EB)

### Epidermolysis bullosa (Table 4-10)

Epidermolysis bullosa (EB) is a group of heterogeneously inherited mechanobullous disorders that are manifested as fragile skin leading to blisters. There are four major forms of EB, which are categorized by the level of blister cleavage. The fourth major form, Kindler syndrome, was added to the classification system of EB in 2008.

- EB simplex: **intraepidermal** blister
- Junctional EB: blister through the **lamina lucida** of the BMZ
- Dystrophic EB: blister **below the lamina densa**
- Kindler: mixed levels

Congenital localized absence of skin (CLAS) may be associated with any of the subtypes of EB. Previously this was termed Bart syndrome, but that eponym is no longer used in the current classification system.

The diagnosis of EB is made through ultrastructural evaluation of the cleavage plane of the blister and accompanying immunohistochemistry. **It is important that the biopsy specimen is obtained from an induced blister, rather than from a preexisting blister, in order to obtain an accurate result of the level of the split.** Electron microscopy (EM) is the gold standard, but is not as readily available. Thus, immunofluorescence mapping (IFM) is the more commonly used method for diagnosing EB. Once a subtype of EB is identified, genetic analysis may be pursued.

## 4.5 TUMOR SYNDROMES

- Note: Muir-Torre syndrome, dyskeratosis congenita, Peutz-Jeghers syndrome, and xeroderma pigmentosum are discussed elsewhere

### Basal cell nevus syndrome (BCNS; Gorlin syndrome)

- **AD mutations in the *PTCH* gene** (encodes the patched tumor suppressor protein of sonic hedgehog signaling pathway)
  - Patched normally inhibits smoothened (which, when uninhibited, signals intracellularly to activate *GLI1/2*

(transcription factors) to promote transcription of genes involved in cellular growth)

- Mutations in *PTCH* → dysregulation of smoothened and ↑transcription of *GLI* genes → neoplasia
- Diagnostic criteria include the presence of one major criterion + molecular confirmation, two major criteria, or one major and two minor criteria.
  - **Major criteria:**
    - Basal cell carcinomas (BCC) (>2 BCC or 1 before 20 years of age)
      - ◆ Multiple, early onset (typically around puberty)
      - ◆ May resemble melanocytic nevi, milia, acrochordons, or seborrheic keratoses
      - ◆ Favor sun-exposed areas (face, neck, and upper torso), but can occur in sun-protected sites
    - **Palmoplantar pits** (>3), often present in childhood
    - **Odontogenic keratocysts of the jaw**, histologically proven
      - ◆ Generally asymptomatic
      - ◆ Typically present late in the first decade of life
    - **Calcification of the falx cerebri**
    - **Medulloblastoma**, which typically presents within the first three years of life
    - First-degree relative with BCNS
  - **Minor criteria:**
    - Rib anomalies (**bifid**, fused, or markedly splayed)
    - Cleft lip/palate
    - Other skeletal anomalies (pectus excavatum or pectus carinatum, polydactyly, syndactyly, kyphoscoliosis, Sprengel deformity, or other vertebral anomalies)
    - Macrocephaly
      - ◆ **Frontal bossing**, a broad nasal root, and hypertelorism may be seen
    - **Ovarian/cardiac fibroma**
    - Lymphomesenteric cysts
    - Ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, and colobomas)
  - Other features include: increased risk of fibrosarcoma and rhabdomyosarcoma, cryptorchidism, gynecomastia, agenesis of corpus callosum, **ovarian fibromas**, and cardiac fibromas
- Treatment: standard BCC treatment methods +/- targeted therapy with **vismodegib**, a smoothened inhibitor (essentially acts as "artificial *PTCH*")
- **Syndromes a/w multiple BCCs (Boards favorite!):** Gorlin, Bazex-Dupré-Christol, Rombo, Brooke-Spiegler, xeroderma pigmentosum, and Schöpf-Schulz-Passarge

### Birt-Hogg-Dubé syndrome

- AD disorder as a result of mutations in *BHD* gene (encodes **folliculin**)
- Manifestations begin in third decade or later
- Cutaneous findings: **fibrofolliculomas**, **trichodiscomas**, and **acrochordons**
  - Fibrofolliculomas/trichodiscomas appear as multiple tiny skin-colored to white papules on the face
  - On histology, fibrofolliculomas/trichodiscomas have slender strands of basophilic cells radiating from a follicular unit, surrounded by a fibrous stroma

**Table 4-10.** Types of Epidermolysis Bullosa

<b>EB Simplex (EBS)</b> <ul style="list-style-type: none"> <li>• Level of split is intraepidermal</li> <li>• Most common form of EB</li> <li>• AD inheritance, except for EBS with muscular dystrophy (AR)</li> <li>• Bullae generally heal without scarring</li> </ul>							
Subtype	Mode of Inheritance	Gene(s)	Protein(s)	Onset	Primary Cutaneous Features	Associated Clinical Features	Prognosis
EBS-localized (previously called Weber-Cockayne)	AD	<i>KRT5</i> <i>KRT14</i>	Keratin 5 Keratin 14	Birth through adolescence	Tense bullae predominantly on <b>hands and feet</b> , soles > palms (Fig. 4-12); non-scarring Worse with heat, ill-fitting shoes, and frictional trauma from walking	Rare oral blisters early in life Occasional palmoplantar hyperkeratosis Rare nail dystrophy	<b>Normal life span</b> May have worse blisters and severe pain during summer months
EBS-generalized intermediate (previously known as Koebner)	AD	<i>KRT5</i> <i>KRT14</i>	Keratin 5 Keratin 14	Birth or infancy	Tense bullae at <b>any site of friction</b> ; non-scarring Bullae worse with heat	May have oral blisters Palmoplantar hyperkeratosis over time May have nail dystrophy	Normal life span
EBS-generalized severe (previously known as Dowling-Meara or EBS herpetiformis)	AD	<i>KRT5</i> <i>KRT14</i>	Keratin 5 Keratin 14	Birth, or within first few weeks of life	<b>Generalized blisters</b> After first few months of life, bullae take on characteristic <b>clustered herpetiformis appearance</b> May rarely heal with some scarring and milia	Oral blisters common Nail shedding, <b>nail dystrophy</b> and hyperkeratotic nails are common <b>Palmoplantar hyperkeratosis</b> Characteristic <b>clumped tonofilaments</b> on electron microscopy	<b>Most severe form of EBS</b> Usually normal life span Rare associated early death due to <b>sepsis</b> , anemia, or growth failure
EBS-mottled pigmentation	AD	<i>KRT5</i> <i>KRT14</i>	Keratin 5 Keratin 14	Childhood	Acral blisters <b>Mottled hyperpigmentation</b> on the trunk and limbs	Punctate palmoplantar keratoderma Common nail dystrophy	Very rare subtype, normal life span
EBS-muscular dystrophy	<b>AR</b>	<i>PLEC</i>	<b>Plectin</b>	Bulla develop at birth, but <b>muscle weakness is delayed</b> (may develop in infancy through adulthood)	Generalized blisters that lead to atrophic scars	Muscular dystrophy with onset in infancy or later in life Common nail hyperkeratosis Common dental abnormalities Associated cerebral and cerebellar atrophy, urethral stricture, and scarring alopecia	Morbidity from muscular dystrophy
<b>Junctional EB (JEB)</b> <ul style="list-style-type: none"> <li>• Cleavage plane of blister is within the lamina lucida of the BMZ</li> <li>• Rarest form of EB</li> <li>• AR inheritance</li> <li>• Enamel hypoplasia/pitting (and possible tooth loss due to caries) occurs in all forms of JEB</li> </ul>							
Subtype	Mode of Inheritance	Gene(s)	Protein(s)	Onset	Primary Cutaneous Features	Associated Clinical Features	Prognosis
JEB-generalized severe (previously known as JEB-Herlitz or EB Lethalis)	AR	<i>LAMA3</i> <i>LAMB3</i> <i>LAMC2</i>	<b>Laminin 332</b> (premature termination codon)	Birth	Generalized blisters; typically heals <b>without scarring</b> Common sites are <b>buttocks, perioral</b> , and pinnae of ears	Oral blisters common <b>Hoarse cry</b> as a result of <b>laryngeal involvement</b> Paronychia inflammation with nail dystrophy and nail loss Granulation tissue of nail beds <b>Perioral granulation</b> tissue may develop beyond 6 months of age	<b>Death</b> within first few years of life from <b>respiratory failure</b> or <b>septicemia</b> (90% die by age 1 year) Failure to thrive and anemia very common

Continued



**Table 4-10.** Types of Epidermolysis Bullosa—cont'd

Subtype	Mode of Inheritance	Gene(s)	Protein(s)	Onset	Primary Cutaneous Features	Associated Clinical Features	Prognosis
JEB-generalized intermediate (previously known as non-Herlitz, generalized atrophic benign EB)	AR	LAMA3 LAMB3 LAMC2 COL17A1	Laminin 332 Collagen XVII (BPAG2/BP180)	Birth	Generalized blisters and oral involvement common in neonatal period, but improves as child ages; heals with <b>atrophic scars</b> Granulation tissue uncommon	<b>Scarring alopecia</b> Nail dystrophy common Dental enamel hypoplasia common Corneal erosions	Survival to adulthood
JEB-pyloric atresia	AR	ITGA6 ITGB4	$\alpha 6\beta 4$ integrin	Birth	Generalized blisters, often with large areas of congenital localized absence of skin	<b>Pyloric atresia</b> Scarring of urinary tract, leading to <b>ureteral stenosis</b> and hydronephrosis (requires urologic surgery) Rudimentary and malformed ears	Poor prognosis with mortality in infancy
<p align="center"><b>Dystrophic EB (DEB)</b></p> <ul style="list-style-type: none"> <li>• Level of split is below the lamina densa of the BMZ</li> <li>• Two major subtypes are categorized by mode of inheritance: dominant dystrophic EB (DDEB) and recessive dystrophic EB (RDEB)</li> <li>• In general, DDEB is more mild than RDEB, though there is considerable overlap between the milder forms of RDEB and DDEB</li> <li>• DDEB may rarely manifest with only nail dystrophy</li> </ul>							
Subtype	Mode of Inheritance	Gene(s)	Protein(s)	Onset	Primary Cutaneous Features	Associated Clinical Features	Prognosis
DDEB	AD	COL7A1 (missense mutation)	Collagen VII	Birth	<u>Cockayne-Touraine Type</u> : Generalized bullae, most prominent overlying extensor joints; tends to improve over time; heals with <b>atrophic scarring and milia</b> <u>Pasini Type</u> : Similar to Cockayne-Touraine type but also has scar-like <b>"allopapuloid" papules</b> that favor trunk and arise spontaneously (without preceding blisters)	<b>Nail dystrophy common</b> Oral blisters may occur Rarely may have esophageal strictures Anemia uncommon	Disease activity tends to improve over time
RDEB, generalized severe (previously known as Hallopeau-Siemens)	AR	COL7A1 (premature termination codon leads to complete <b>lack of anchoring fibrils</b> )	Collagen VII	Birth	Generalized mucocutaneous blisters (Fig. 4-13) <b>Heals with atrophic scarring and milia</b>	<b>Pseudosyndactyly ("mitten deformities" of hands/feet) common</b> and pathognomonic <b>Contractures of digits and limbs</b> Scarring alopecia Corneal erosions Oral blisters common Microstomia Dental caries (severe) Esophageal strictures and other GI complications common Osteopenia Growth failure Anemia Dilated cardiomyopathy may (rarely) occur <b>Renal failure</b> <b>Aggressive SCC</b>	Many comorbidities of other organ systems <b>SCC is leading cause of death</b> (affects 50% of pts by age 35yo) Renal failure (12% mortality)

**Table 4-10.** Types of Epidermolysis Bullosa—cont'd

Subtype	Mode of Inheritance	Gene(s)	Protein(s)	Onset	Primary Cutaneous Features	Associated Clinical Features	Prognosis
RDEB, generalized intermediate (previously known as non-Hallopeau-Siemens type)	AR	COL7A1	Collagen VII	Birth	Generalized blisters Heals with atrophic scars and milia May be difficult to distinguish from DDEB clinically	Fewer comorbidities than the severe form of RDEB	Like DDEB, disease activity may improve slightly over time
<p align="center"><b>Kindler Syndrome (Acrokeratotic poikiloderma)</b></p> <ul style="list-style-type: none"> <li>• Rare disorder characterized by skin fragility, photosensitivity, and poikiloderma</li> <li>• In 2008, this disorder was grouped as a major form of EB, with mixed blister cleavage plane</li> <li>• Immunohistochemical analysis shows reduced or absent staining against fermitin family homolog 1 (<b>FERMT1</b> gene, formerly known as kindlin-1; protein involved in keratinocyte adhesion and migration)</li> <li>• Electron microscopy shows <b>duplication of the lamina densa</b>; histology shows absence/fragmentation of elastic fibers</li> </ul>							
Kindler syndrome	AR	<i>FERMT1</i>	Fermitin family homolog 1	Neonatal period	<b>Poikiloderma</b> <b>Acral blisters</b> , though may have more widespread involvement	<b>Photosensitivity</b> Palmoplantar hyperkeratosis Nail dystrophy SCC of the lip and hard palate	Skin fragility, photosensitivity usually improves over time



**Figure 4-12.** EB simplex, localized type. Note the superficial blistering with both intact bullae and denuded skin. This form tends to be limited to the palms and soles. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier, 2011)



**Figure 4-13.** Recessive dystrophic epidermolysis bullosa in a neonate. (Personal collection, Phuong Khuu)

- Systemic findings: **renal cell carcinoma** and **spontaneous recurrent pneumothorax** (w/ lung cysts and bullous emphysema)

### Brooke-Spiegler syndrome

- AD disorder as a result of mutations in cylindromatosis (**CYLD**) gene (a tumor suppressor); **CYLD** is a deubiquinating enzyme that normally interacts with NEMO to downregulate NFκB expression
- Skin findings (presenting in adolescence/early adulthood): **cylindromas** (papules/nodules on scalp), **trichoepitheliomas** (skin-colored to white small facial papules), **spiradenomas** (painful nodules on head/neck and elsewhere), and multiple BCCs; malignant

degeneration into cylindro- and spiradenocarcinoma may occur (increased risk compared to general population)

- Extracutaneous findings: **salivary and parotid gland tumors**

### Multiple endocrine neoplasia (MEN) syndromes

- **MEN I (Wermer)**
  - AD disorder as a result of mutations in **MEN1** gene (menin)
  - Tumors in pituitary (esp. prolactinoma), parathyroid (usually hyperplasia or adenoma) and pancreas (usually islet cell hyperplasia, adenoma, or carcinoma) [3 Ps = mnemonic]

- Cutaneous findings may be similar to tuberous sclerosis – facial angiofibromas, gingival papules, hypopigmented macules, and CALM
- **MEN IIA (Sipple)**
  - AD disorder as a result of mutations in the *RET* proto-oncogene
  - **Parathyroid hyperplasia** (not seen in MEN IIB) + **medullary thyroid carcinoma** (~100%) + **pheochromocytoma**
  - Cutaneous findings: **lichen amyloidosis and macular amyloidosis** (+/- nostalgia paresthetica)
- **MEN IIB (multiple mucosal neuroma syndrome)**
  - AD disorder as a result of mutations in *RET*
  - Skin findings: **mucosal neuromas on tongue/lips**, thickened lips, and **marfanoid habitus**
  - Endocrine findings: **medullary thyroid carcinoma** (~100%; fatal if not caught early!) and **pheochromocytoma**
  - Ocular findings: conjunctival neuromas → thickened/everted upper eyelids
  - GI findings: ganglioneuromatosis → megacolon, diarrhea, and constipation

### Cowden syndrome (multiple hamartoma syndrome)

- AD disorder as a result of mutations in the *PTEN* tumor suppressor gene → proliferation of cutaneous/GI/mucosal/thyroid/breast tissues; manifestations begin in second to third decade
- *PTEN* is also mutated in Bannayan-Riley-Ruvalcaba syndrome (has many features of Cowden syndrome + pigmented macules on glans penis, lipomas, macrocephaly and mental retardation) and rare cases of Proteus syndrome (most cases now known to be caused by *AKT1* gene)
- Cutaneous findings: **sclerotic fibromas**, **facial tricholemmomas** (skin-colored to light brown small papules), **punctate palmo-plantar keratoses**, **keratotic papules (acral keratoses)** on dorsal hands/feet/forearms/legs, **lipomas**, skin tags, and inverted follicular keratoses
- Oral findings: small skin-colored grouped papillomas → “cobblestone” appearance on lips and gingival/buccal/labial mucosa
- Thyroid findings: goiter, adenomas, and carcinoma (follicular carcinoma is most common type)
- Breast findings: fibrocystic disease, fibroadenomas, and **adenocarcinoma (most common malignancy overall; in up to 50% of female patients)**
- GI findings: **hamartomatous polyps** along GI tract (most common in colon) – low risk of malignant transformation
- Other findings: ovarian cysts (benign), uterine leiomyomas, **endometrial carcinoma** (in up to 10% of female patients), menstrual irregularities, various GU carcinomas/cysts, **craniomegaly** (>80% of patients), adenoid facies, kyphoscoliosis, bone cysts, large hands/feet, myopia, angioid streaks, and intracranial venous anomalies
- **Lhermitte-Duclos disease** (dysplastic gangliocytoma of cerebellum): pathognomonic criterion for Cowden’s; p/w overgrowth of cerebellar ganglion cells → ataxia, seizures and ↑intracranial pressure

### Gardner syndrome

- AD mutations in adenomatous polyposis coli (*APC*) gene (tumor suppressor gene that regulates β-catenin)
- Cutaneous manifestations: **epidermoid cysts** (classically with **pilomatricoma changes**), fibromas (skin/subcutaneous/mesentery/retroperitoneum), lipomas
- GI manifestations:
  - Premalignant polyposis throughout GI tract → ↑↑↑risk **adenocarcinoma** (esp. colon/rectum; ~100% affected)
  - **Desmoid tumors**: locally aggressive, but do not metastasize; female > male; may arise post-surgically after colectomy; can → small bowel and/or ureter obstruction
- Ocular manifestations: congenital hypertrophy of retinal pigment epithelium (**CHRPE**; 70%)
- Other findings: **osteomas** (skull/mandible/maxilla; 80% patients; painless), odontomas of teeth, supernumerary teeth, papillary thyroid carcinoma (women), hepatoblastoma, adrenal adenomas, sarcomas, pancreatic carcinomas, and brain tumors (e.g., glioblastomas and medulloblastomas; in subtype of Gardner syndrome called Turcot syndrome)
- **Treatment = prophylactic colectomy** when polyp formation is first evident (2nd–3rd decade)

## 4.6 VASCULAR TUMORS, MALFORMATIONS, AND RELATED VASCULAR DISORDERS

### Vascular tumors

Vascular tumors are discussed more extensively in the Neoplastic Dermatology Chapter.

### PHACE syndrome

- **Female predominance 9:1**
- Large segmental hemangioma on head/neck (**V1-V3 distribution**)
- **Cerebrovascular anomalies most common extracutaneous finding**
  - Those with frontotemporal segment involvement may be at most risk of cerebrovascular abnormalities
  - Those with mandibular segment involvement may be at most risk of cardiac defects
- Posterior fossa malformations (e.g., Dandy-Walker and cerebellar hypoplasia)
- Hemangioma, segmental
- Arterial anomalies (internal carotid arteries and cerebral arteries)
- Cardiac anomalies (**coarctation of aorta**, ventral and atrial septal defects, and patent ductus arteriosus)
- Eye anomalies (microphthalmos, optic atrophy, **cataracts**, strabismus, and exophthalmos)
- Sternal cleft or supraumbilical raphe



Figure 4-14. LUMBAR (SACRAL) syndrome. (Personal collection, Dr. Jane Bellet)

- MRI/MRA of head and neck to evaluate for cerebrovascular anomalies
- **Oral propranolol is first-line therapy**, though coarctation of the aorta or other significant congenital heart disease should be ruled out before starting therapy

### LUMBAR/SACRAL syndrome

- Segmental hemangioma of the **lower back** (lumbar or sacral spine) or buttocks and genitalia (Fig. 4-14)
- Lower body hemangioma
- Urogenital anomalies/ulcerations
- Myelopathy (myelomeningocele)
- Bony deformities
- Anorectal malformation
- Renal anomalies
- Spinal dysraphism
- Anogenital anomalies
- Cutaneous anomalies
- Renal and anal anomalies
- Angioma with Lumbosacral location
- If a segmental hemangioma crosses over the midline lower spine, imaging is required. Ultrasound can be done in very young infants; however, MRI of the spine is the gold standard.
- **Propranolol** should be considered for large, ulcerated, or otherwise complicated segmental hemangiomas

### Neonatal hemangiomatosis

- **Benign neonatal hemangiomatosis:**  $\geq 5$  hemangiomas; hemangiomas are small, localized, and limited to the skin
- **Diffuse neonatal hemangiomatosis:**  $\geq 5$  hemangiomas with organ involvement (esp. liver, but may also be intestines, brain, eyes, spleen, kidney, and lungs)
  - For patients with significant visceral involvement leading to **liver failure and/or high output congestive heart failure**, propranolol is first-line therapy
  - Large liver hemangiomas may cause hepatomegaly and congestive heart failure

### Kasabach-Merritt phenomenon

- Usually occurs in the first few weeks to months of life
- Occurs in association with **tufted angioma** or **kaposiform hemangioendothelioma**
- Pathogenesis: abnormal endothelium and convoluted architecture of KHE or tufted angioma promote platelet adhesion and trapping with subsequent **consumptive coagulopathy**
- Sudden growth of a vascular lesion with induration, edema, and advancing purpuric edge
  - Severe thrombocytopenia (from platelet trapping), consumptive coagulopathy, hypofibrinogenemia, elevated D-dimer, hemolytic anemia, and DIC
  - Hematuria, hematochezia, and epistaxis may occur
  - High output cardiac failure and significant risk of internal hemorrhage → **10–30% mortality**
- **Systemic corticosteroids and vincristine** are primary therapeutic interventions. Systemic sirolimus is an emerging treatment in this setting. Response to Propranolol has been poor

### Vascular malformations

#### Capillary malformations

#### Capillary malformation (“Port Wine Stain,” PWS, nevus flammeus)

- Sporadic, affecting 0.1%–2% of newborns
- Unknown pathogenesis; mutations in *GNAQ* reported
- Red-purple vascular macule or patch **present at birth**
- Often located on the face, but may be found anywhere on the body
- Usually an isolated cutaneous finding, but may be seen in **several syndromes** (Sturge-Weber syndrome, Klippel-Trenaunay syndrome, Parkes-Weber syndrome, Proteus, PTEN hamartoma syndromes, Cobb syndrome, Beckwith-Wiedemann syndrome, phakomatosis pigmentovascularis, and capillary malformation-arteriovenous malformation [CM-AVM])
- On histology, dilated venules in dermis with normal number of vessels and no endothelial proliferation (is a malformation rather than true neoplasm)
  - In adults, fibrosis around the vessels and vascular dilation can be seen
- **Pulsed dye laser = first-line therapy**
- Lesions do not fade spontaneously; ↑ in size proportionately to the child’s growth; may become gradually darker and hypertrophic over time

#### Sturge-Weber syndrome (SWS) (encephalotrigeminal angiomatosis)

- 2° to somatic mosaic mutations in the *GNAQ* gene
- Capillary malformation in V1 (ophthalmic branch of trigeminal nerve) and V2 (>V3) distribution (Fig. 4-15)
  - Only 10% with a V1 capillary malformation will have SWS
  - Unilateral > bilateral
  - Soft tissue/skeletal hypertrophy under malformation





**Figure 4-15.** Sturge-Weber syndrome. This patient has a classic diffuse capillary hemangioma in the distribution of the ophthalmic, nasociliary, and maxillary branches of the trigeminal nerve. The lesion extends backward over the anterior two thirds of the crown of the head. (From Forbes CD, Jackson WD. Color Atlas and Text of Clinical Medicine. 2nd ed. London: Mosby; 1996.)

- Ipsilateral leptomeningeal capillary malformation (angiomatosis) of the brain and eye
- Neurologic complications include **seizures** (usually develop in first year of life), developmental delay, intellectual disability, and focal neurologic deficits
  - Head CT = cortical calcifications that resemble “tram track lines”
- Ophthalmologic complications affect 60% (#1 is **glaucoma**)
- Clinical course depends on extent of leptomeningeal involvement
- Bilateral facial capillary malformations involving V1 distribution = worst prognosis (↑risk of seizures and more profound developmental delay)

### Phakomatosis pigmentovascularis

- Widespread capillary malformation in addition to other cutaneous findings
- Five defined types, a = no extracutaneous involvement; b = extracutaneous involvement
  - I: PWS + epidermal nevus
  - II (phakomatosis cesioflammea): PWS + **dermal melanocytosis** +/- nevus anemicus; **most common** form (85%); roughly 50% have major complications (Sturge-Weber, Parkes-Weber, or KTS)
  - III (phakomatosis spiliorosa): PWS + **nevus spilus** +/- nevus anemicus
  - IV: PWS + dermal melanocytosis + nevus spilus +/- nevus anemicus
  - V (phakomatosis cesiomarmorata): cutis marmorata telangiectatica congenita + dermal melanocytosis
- Extracutaneous features include neurologic, musculoskeletal, and ocular findings

### Phakomatosis pigmentokeratotica

- 2° to post-zygotic mutation in *HRAS*
- **Speckled lentiginous nevus (nevus spilus) in conjunction with nevus sebaceus**
  - Neoplasms (**Trichoblastoma** > SPAP > BCC) may develop within nevus sebaceus
- Neurologic abnormalities may be present and include seizures, hemiparesis, and intellectual impairment
- Hyperhidrosis, neuropathy, and muscle weakness can be seen
- **Hypophosphatemic vitamin D-resistant rickets** can develop

### Klippel-Trenaunay syndrome

- Recently reported association with mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*)
- Capillary malformation, venous malformation, and/or lymphatic malformation with soft tissue and/or bone **hypertrophy** of one limb
  - **Lower extremities** (95%) are affected much more commonly than upper extremities
  - Venous varicosities are common
- Complications include deep vein thrombosis and thrombophlebitis, pulmonary embolism, GI bleeding, vascular blebs and pain, and **high-output cardiac failure**

### Proteus Syndrome

- Previously was thought to be due to *PTEN* mutations, but now known to be 2° to *AKT1* **somatic activating mutation** → asymmetric progressive overgrowth
- Skin:
  - **Cerebriform connective tissue nevi** (plantar collagenoma): pathognomonic if present
  - **Capillary/venous/lymphatic malformations**
  - Epidermal nevi
  - Lipomas
  - CALM
  - Focal atrophy/dermal hypoplasia
  - Varicosities
  - Partial lipohypoplasia
- CNS: hemimegalencephaly and **impaired intelligence**
- Ophthalmologic: nystagmus, strabismus, cataracts, and myopia
- Musculoskeletal
  - Typical facies: dolichocephaly, down-slanting palpebral fissures, depressed nasal bridge, anteverted nares, and open mouth position at rest
  - **Overgrowth** of one or more of the following (involves soft tissue and bone): **extremities, digits, cranium** (hemifacial macrosomia), vertebrae, and external auditory meatus
  - Hyperostoses
  - Scoliosis
- **Bilateral ovarian cystadenoma** and parotid monomorphic adenoma
- **Organomegaly**
- Cystic lung malformations
  - Restrictive lung disease
  - Pulmonary emphysema
  - Recurrent pneumonia
- Risk of venous thrombosis and pulmonary embolism

### Beckwith-Wiedemann syndrome

- Associated with chromosome 11 abnormalities at **p57(*KIP2*) gene**
- 85% of cases are sporadic
- Clinical features:
  - **Macrosomia/gigantism** (height and weight >97%)
  - **Facial capillary malformation** of glabella, mid-forehead, and upper eyelids
  - **Hemihyperplasia** (asymmetric overgrowth)
  - **Macroglossia**
  - **Omphalocele/exomphalos**
  - Anterior **linear earlobe creases** and posterior helical ear pits
  - **Visceromegaly** (kidney, liver, pancreas, spleen, and heart)
  - Neonatal hypoglycemia
- ↑risk for embryonal tumors (**Wilms' tumor** (#1), rhabdomyosarcoma, neuroblastoma, and hepatoblastoma)

### Macrocephaly capillary malformation syndrome

- Mutations in *AKT3*, *PIK3CA*, or *PIK3R2*
- Macrocephaly and frontal bossing
- Widespread reticulated capillary malformation often involving **mid-face** (philtrum and glabella)
- **Hemihypertrophy** involving contralateral side of the body from the capillary malformation
- **Progressive neurologic dysfunction** → developmental delay, seizures, and hypotonia
  - Polymicrogyria, cerebral asymmetry, white matter abnormalities, ventriculomegaly, cortical dysplasia, and/or cerebellar tonsillar herniation
- **Syndactyly** (especially second-third toes), polydactyly, joint laxity, and hyperplastic skin
- ↑risk of Wilms' tumor

### Venous malformations

- Sporadic, but 50% of sporadic VMs have *TIE2* (aka *TEK*) mutations
  - Familial cutaneous and mucosal venous malformation syndrome (VMCM): widespread VMs of skin, mucosa and visceral organs due to *TIE2* (aka *TEK*) mutations; has significant overlap w/Blue rubber bleb syndrome!
- Present at birth, but may become more apparent childhood
- Erythematous to violaceous, soft, compressible nodule or plaque without warmth, vascular thrill, or pulsations +/- radiating veins
- On histology, dilated vascular spaces with single-layer endothelial wall that is surrounded by fibrous tissue; involves deep dermis or subcutaneous fat
- Ultrasound shows **slow flow lesion**; MRI is best imaging modality to determine extent; on plain films, calcification can be seen 2° to phleboliths; fibrinogen may be ↓ and D-dimer may be ↑

### Maffucci syndrome (Enchondromas with multiple angiomas)

- Previously thought to be due to mutations in *PTHRI* (parathyroid hormone related protein); but OMIM states that most (80%) cases are now known to be caused by mutations in isocitrate dehydrogenase (*IDH1* and *IDH2*); characterized by mesodermal dysplasia of skin and skeletal systems
- First sign in early infancy = deep venous malformations (soft, compressible, and bluish nodules) on the **hands and feet**
- **Enchondromas** develop on the phalanges and long bones, and predispose to **short stature, fractures**, and limb length discrepancies; can occur in cranium/vertebrae → neurological problems
- Lymphatic malformations, hemangioendotheliomas, and spindle cell hemangiomas may be present
- Extracutaneous sites of vascular malformations: leptomeninges, eyes, oropharynx, and GI tract
- Clinical course: bone fractures secondary to non-ossification; **50% risk for chondrosarcoma (occurs within enchondromas)**; lymphangiosarcoma and hemangiosarcoma also reported

### Blue-rubber bleb nevus syndrome

- Usually sporadic
- Presents at birth to early childhood with venous malformations (**multiple blue-violaceous compressible papules and nodules** with hyperhidrosis overlying lesions; with compression, an empty wrinkled sac is noted that quickly fills with release of pressure)
  - Venous malformations involve the **trunk/extremities, mucosa, GI tract** (esp. small intestine), liver, and CNS
  - ↑size/# with age
- On histology, ectatic vascular spaces with single-layer endothelial wall that is surrounded by fibrous tissue, usually well-circumscribed, and are seen in the deep dermis or subcutaneous fat
- **Small intestine blebs** → hemorrhage (which may → death if severe) or occult/chronic bleeding (melena and iron deficiency anemia)

### Glomulovenous malformations (GVM; previously termed "glomangiomas")

- Variant of venous malformation (is not a neoplasm → no longer referred to as "glomangioma") where ectatic vessels are lined by a small number of glomus cells
  - Glomus cells are modified smooth muscle cells of **Sucquet-Hoyer canal** origin
  - **AD inheritance**, due to loss of function mutations in **glomulin (*GLMN*) gene**
- Clinical presentation: presents in **infancy** or childhood with **multiple lesions** (soft, partially compressible blue nodules > confluent plaques); favors **lower extremities**; usually **asymptomatic** (pain is more common with glomus tumors)
- Histology: large, dilated vessels surrounded by a small number of glomus cells

- Treatment: Sclerotherapy, CO<sub>2</sub> laser, and Nd:YAG laser may help
  - Surgical excision generally not feasible for GVM, since multiple lesions and high rate of recurrence
- Comparison with glomus tumor
  - Glomus tumor: **more common** (accounts for 80% of all glomus lesions); affects **young adults** (20–40 yo); **solitary** blue papule or nodule with triad of **tenderness, sensitivity to cold, and paroxysmal pain**; most common on palms and **subungual area** (may result in bony erosion); histology shows dense proliferation of **many glomus cells** surrounding small vascular spaces; easily treated with excision

## Lymphatic malformations

### Microcystic lymphatic malformations (superficial lymphatic malformation, “lymphangioma circumscriptum”)

- More common than macrocystic lymphatic malformations
- Present in first few months to years of life
- Always **confined to one anatomic region**; most common sites = **abdomen**, axillae, mouth (esp. **tongue**), and genital region
- Presents w/ **clusters of papulovesicles** with clear or **blood-tinged** fluid (red-purple in color), either discrete or coalescing into a plaque, resembling “**frog spawn**” (Fig. 4-16)
- On histology, collections of small dilated lymphatic channels in the dermis are lined by endothelial cells
  - D2-40 (podoplanin) and LYVE-1 positive
- Can perform surgical excision, sclerotherapy or destructive measures (CO<sub>2</sub> or pulsed-dye lasers) for localized lesions

### Macrocystic lymphatic malformations (cystic hygroma)

- Congenital lesions are thought to result from abnormal lymphatic development during embryogenesis



**Figure 4-16.** Microcystic lymphatic malformation – irregularly grouped, translucent, and red papules. (From Marks JG, Miller JJ. Lookingbill and Marks' Principles of Dermatology, 5th Ed. Elsevier. 2013)

- Associated with fetal aneuploidy, including **Turner syndrome and Down syndrome**; also associated with Noonan syndrome and achondroplasia
- Majority (~60%) are present at birth
- Presents as a large, soft, bluish, and sometimes translucent tumor, with normal overlying skin
  - Transilluminates with light
  - Head, neck, and axilla/chest most common locations, favoring left side
- Sudden size ↑ may herald infection or intralesional hemorrhage
- On histology, large, multicystic, irregular lymphatic sinuses with a single layer endothelial lining, a fibrous adventitia, and both smooth and striated muscle component
  - D2-40 (podoplanin) and LYVE-1 positive
- Mortality (<6%), usually as a result of airway obstruction or pneumonia
- Complications include pleural/abdominal/pericardial effusions, lymphedema, cardiac failure, and respiratory failure

### Congenital lymphedema (hereditary congenital lymphedema, Nonne-Milroy syndrome)

- **Female > male**
- Developmental aplasia, hypoplasia, and/or functional failure of lymphatic vessels
- **AD inheritance**; due to loss-of-function mutations in **FLT4 gene** (encodes VEGFR3, which is required for lymphatic development)
- Presents at birth (or soon after) and persists for life
- Painless pitting edema of **bilateral lower extremities**
  - Over time, involved area becomes firm and fibrotic
  - Associated features: **hydrocele**, prominent veins, and upslanting toenails
- Treatment options: good skin hygiene, stop medications/activities that promote dependent edema, massage (manual lymphatic drainage) and use of compression garments, and surgical interventions (microvascular lympholymphatic anastomosis, staged excision, and total superficial lymphangiectomy)
- Contrast with **Lymphedema-distichiasis syndrome**: also a form of hereditary lymphedema but has **peripubertal-onset** (10–30yo); **AD inheritance**; **FOXC2** mutation; lower-limb lymphedema + distichiasis (extra eyelashes ranging from a single hair to a full set)

## Arteriovenous malformations (AVMs)

### AVMs

- Rarest but most dangerous type of vascular malformation
- Developmental anomaly arising early in embryogenesis → abnormal communication between an artery and vein causing high-flow (**fast-flow**) shunting of blood from the arterial circulation to the venous circulation (AV shunting)
- Erythematous to violaceous patches/nodules/tumors that are warm to touch and have **palpable thrill or pulsation**; most commonly **cephalic** (70%)



- Peripheral edema, pain, varicosities, ulceration, and limb hypertrophy may develop
- Small, hemodynamically stable AVMs are asymptomatic, but larger, hemodynamically unstable AVMs may → tachycardia/congestive heart failures
- Puberty, pregnancy and trauma are common exacerbating factors
- MRI and ultrasound studies confirm diagnosis and assess disease extent
- On histology, circumscribed, unencapsulated, and thick-walled arterioles w/direct connection to veins (thin-walled), and abundant superficial capillaries
- Embolization + excision is the treatment of choice for symptomatic lesions; amputation may be required as a result of aggressive growth
- Consumptive coagulopathy may develop in larger AVM

### Parkes-Weber syndrome

- Mutations in *RASA1* have been noted
- Characterized by capillary malformations, venous malformations, lymphatic malformations, and multiple fast-flow arteriovenous malformations/shunts (differentiates it from Klippel-Trenaunay syndrome, which only has slow-flow malformations)
- Typically affects the lower extremities
  - Soft tissue and bony hypertrophy
- On histology, circumscribed, unencapsulated, and thick walled vessels (mixture of markedly abnormal arteries and veins; internal elastic lamina of the arteries may be reduplicated, interrupted, and distorted; the muscularis media varies greatly in thickness)
- Duplex ultrasound and MRI/MRA may be needed to differentiate from Klippel-Trenaunay syndrome
- High output cardiac failure can occur in infancy or later in life
- The development of lytic bone lesions can be seen
- Poor prognosis after puberty with continued growth of the AV malformation

### Cobb syndrome (cutaneomeningospinal angiomatosis)

- Spinal hemangioma or AVM (most common) + cutaneous capillary malformation of the same metamere of the torso
- Cutaneous manifestations: faint erythema (elicited with rubbing the affected area, often with Valsalva maneuver) to violaceous patches and plaques
  - Located on lumbar back
  - Painful throbbing (due to AVM) may develop
- Neurologic abnormalities (due to enlarging AVM, which causes a mass effect on spinal cord) typically develop in childhood and include back pain or headache, muscle atrophy, weakness/numbness, and bowel/bladder dysfunction 2° to spinal compression
- MRI = imaging modality of choice

### Other vascular disorders

#### Cutis marmorata telangiectatica congenita

- Unknown etiology; may represent mosaicism



**Figure 4-17.** Cutis marmorata telangiectatica congenita. The reticulate mottling was limited to the chest in this newborn male. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)

- Present at birth as reticulated erythematous-violaceous vascular network (Fig. 4-17)
  - Usually on lower extremities and unilateral
  - Cold exposure may accentuate cutaneous features
  - Atrophy and ulceration can occur → scarring
  - Often fades over first 2–3 years of life
- Ipsilateral hypertrophy or atrophy may occur (girth and length)
- Neurologic abnormalities in some: seizures, macrocephaly, developmental delay/mental retardation, and/or ophthalmologic anomalies (e.g., glaucoma)
- Adams-Oliver syndrome: CMTC with scalp aplasia cutis congenita and transverse limb defects

### Angiokeratoma corporis diffusum (ACD)

- Finding seen in Fabry disease, fucosidosis, GM1 gangliosidosis, sialidosis, galactosialidosis, aspartylglycosaminuria, and Kanzaki disease
- Histology: numerous thin-walled ectatic blood-filled capillaries in the papillary dermis with a hyperkeratotic epidermis
- Fabry disease:
  - X-linked recessive lysosomal storage disease 2° to deficiency of alpha-galactosidase (*GLA* gene mutation)
    - Glycosphingolipids accumulate in the vascular endothelium and in epithelial, perithelial, and smooth muscle cells of multiple organs (skin, eye, heart, brain, kidney, and peripheral nervous system) → endothelial swelling and proliferation
  - Pubertal males develop thousands of angiokeratomas in “bathing trunk” distribution between umbilicus and knees, as well as oral mucosa/conjunctiva; a/w hypohidrosis
  - “Whorl-like” corneal opacities, and posterior capsular cataracts
  - Episodic and/or chronic paresthesias, often triggered by stress/temperature/fatigue (“Fabry crisis”); often the initial manifestation in early childhood; can develop peripheral neuropathy
  - Cardiac rhythm/conduction abnormalities, cardiomegaly, congestive heart failure, cerebrovascular



accidents, angina/myocardial infarction, peripheral edema, and hypertension

- Renal destruction → polyuria, hematuria, and renal failure
  - Urinalysis typically reveals birefringent lipid globules (“Maltese crosses”)
- Female heterozygotes have much milder presentation (30% w/ ACD; 70% w/ corneal opacities)
- **Recombinant enzyme therapy is the treatment of choice**, and can reverse/delay cardiac, renal, and neurologic complications
  - Progressive neuropathy, renal failure, and cardiac disease
  - Symptomatic strokes in fourth decade, w/ recurrence
  - In patients receiving enzyme replacement, cardiac complications and cerebrovascular disease are the main causes of mortality
- Median age of death = 50 years of age
- Fucosidosis:
  - AR lysosomal storage disease as a result of a mutation/deficiency in  $\alpha$ -L fucosidase
  - ACD occurs earlier in life (around 5 years old) and is more generalized
  - Hypo- or hyperhidrosis, coarse facies, progressive neuromotor and cognitive deterioration/seizures, growth failure, visceromegaly, recurrent infections, and dysostosis multiplex
  - Ultimately fatal
- GM1 gangliosidosis:
  - AR lysosomal storage disease as a result of a mutation/deficiency in  $\beta$ -galactosidase-1
  - Infantile form (type I) presents w/ rapidly progressive hypotonia and neurodegenerative disease, coarse facies, corneal opacities, cherry-red spots on funduscopy, hepatosplenomegaly, and dysostosis multiplex
  - Late infantile/juvenile form (type II) presents later in infancy or early childhood with more gradually progressive neurodegenerative disease
  - Adult-onset form (type III) presents between 3 and 30 years of age w/ progressive extrapyramidal symptoms
  - Cardiomyopathy may develop with any type; ultimately fatal

### Vascular disorders characterized by telangiectasias

(Table 4-11)

## 4.7 DISORDERS OF HAIR AND NAILS

### Pachyonychia congenita

- AD mutations in *KRT6A*, *KRT6B*, *KRT16*, and *KRT17* genes
- Three characteristic features: **onychodystrophy**, **plantar keratoderma**, and **plantar pain**, which develop during childhood
  - Onychodystrophy: discoloration and progressive hyperkeratosis of the nail plate most pronounced at the free edge with a pincer-like appearance (Fig. 4-18)



**Figure 4-18.** Pachyonychia congenita. Nails show progressive discoloration, tenting, and thickening, particularly owing to accumulation of a horny, yellowish brown material of the undersurface that causes the nail to project upward from the nail bed at the free margin. Although unusual, this adolescent's nail changes began during the teenage years. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)

- Painful focal plantar keratoderma with hyperhidrosis and secondary bullae and fissures develop during childhood; palmar involvement is less severe
- Other manifestations may include pilosebaceous cysts, cheilitis, corneal dystrophy, and hoarseness
- Type I: Jadassohn-Lewandowski
  - *KRT6A* and *KRT16*
  - Full expression usually not until late childhood or adulthood
  - Recurrent paronychia
  - **Benign oral leukoplakia** of the tongue and buccal mucosa (vs. premalignant in dyskeratosis congenita)
  - **Follicular hyperkeratosis** of knees, elbows, back, and buttocks
- Type II: Jackson-Lawler
  - *KRT6B* and *KRT17*
  - Natal teeth
  - Minimal oral leukokeratosis
  - **Steatocystomas**
  - Milder keratoderma

### Ectodermal dysplasias

Heterogeneous group of genetic disorders w/ variable abnormalities of hair, teeth, nails, and eccrine glands

### Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)

- XLR mutations in ectodysplasin (*ED1*) classically; AD/AR mutations in ectodysplasin receptor (*EDAR*) and ectodysplasin receptor-associated death domain (*EDARDD*)
  - Female carriers may demonstrate features as a result of random x-inactivation of *ED1* (e.g., alopecia, dental defects, and Blaschkoid linear patches of hypohidrosis)

**Table 4-11.** Vascular Disorders Characterized by Telangiectasias

Diagnosis	Etiology	Key Characteristics of Telangiectasia(s)	Distribution of Telangiectasia(s)	Other Clinical Features
Spider angioma (nevus araneus)	Usually <b>idiopathic in children</b> and not indicative of underlying systemic disorder Associated with <b>liver disease, pregnancy, and estrogen therapy more in adults</b>	Central erythematous papule (arteriole) with radiating linear macules Blanches with diascopy	Most commonly on cheeks, nose, or dorsal hands	None when idiopathic
Unilateral nevoid telangiectasia	Rarely congenital When acquired may be idiopathic or associated with puberty, pregnancy, estrogen therapy, or liver disease	Usually macular, but may have papular center Pallor or vasoconstriction around telangiectasias represents "vascular steal"	Unilateral distribution on upper extremity, trunk, neck, or face May have dermatomal distribution	None when idiopathic
Angioma serpiginosum	Unclear if this represents a vascular malformation or proliferation	Pinpoint red to violaceous papules usually in a serpiginous pattern May be purpuric	Most commonly on <b>lower extremities</b> , but may be more extensive	<b>More common in females (90%)</b>
Generalized essential telangiectasia	Sporadic and idiopathic	Macular, retiform, or linear May coalesce to form large patches	Usually <b>begins on legs</b> and spreads proximally Eventually widespread, but usually spares face	More common in <b>females</b> Slowly progressive May be asymptomatic or associated with paresthesias (numbness, tingling, or burning)
Hereditary benign telangiectasia	AD mutations in <i>TELAB1</i> gene on 5q14	Variable morphology including macular, punctate, or plaque-like Surrounding pallor first appear between 2 and 12 years of age	Predominantly on face, arms, and upper trunk May be on lips and palate	Slowly progressive No associated systemic disease
Hereditary hemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome)	AD mutations in <b>endoglin (HHT1)</b> , activin receptor-like kinase 1 ( <b>ALK1</b> ) ( <b>HHT 2</b> ) or growth/differentiation factor-2 ( <i>GDF2</i> ) gene; other genes may be involved Juvenile polyposis with HHT (JPHH) caused by mutations in <i>SMAD4</i> gene	Dark red and may be elevated May not appear until third or fourth decade of life	Predilection for lips, tongue, palate, nasal mucosa, ears, palms, soles, and nail beds	Most commonly presents with <b>epistaxis</b> (night time) and anemia from GI bleeding <b>AVMs: pulmonary (HHT1 typically), cerebral, and hepatic (HHT2 typically)</b>
Ataxia telangiectasia (Louis-Bar syndrome)	AR mutations in ataxia-telangiectasia mutated ( <b>ATM</b> ) gene (regulates cell cycle control and the cellular damage response to double-strand DNA breaks and confers radiosensitivity and chromosomal instability) – see ↑chromosomal breakage <i>in vitro</i> w/ ionizing radiation <b>Of note, female carriers of the ATM gene have ↑ risk of breast cancer</b>	<b>Oculocutaneous telangiectasias</b> appear around 3–5 years of age Ocular lesions often striking Skin lesions may be subtle and pinpoint Not present in all patients	Typically <b>first appear on bulbar conjunctivae</b> at 3–5 years of age Skin telangiectasias tend to be symmetric and predilection for sun-exposed areas	<b>Truncal ataxia usually first manifestation</b> , followed by choreoathetosis, myoclonus, and oculomotor signs (progressive neurologic deterioration) Other dermatologic manifestations: <b>noninfectious granulomas</b> , progeroid/sclerodermoid changes of skin, hypo- or hyperpigmented patches, and canities Growth failure, thymus hypoplasia, developmental delay, and endocrine anomalies (hypogonadism and diabetes) <b>Immunodeficiency (JlgA/JlgG/JlgE/JlgM)</b> Chronic <b>sinopulmonary infections</b> w/ <i>S. pneumoniae</i> Bronchiectasis → respiratory failure = #1 cause of death (average 20 years of age) <b>↑Risk of malignancies (especially leukemia and lymphoma in adolescence; also breast CA)</b>



**Figure 4-19.** Male patient with hypohidrotic ectodermal dysplasia. Note the flat nasal bridge, depressed nasal tip, sparse hair (scalp, eyebrows, and eyelashes), peg-shaped teeth, full lips, and sebaceous hyperplasia. (Courtesy of Julie V Schaffer, MD. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Clinical triad: ↓sweating, hypotrichosis, and abnormal dentition
  - Facial features: **frontal bossing**, large nostrils, wide/flat malar cheeks, thick everted lower lip, and prominent chin (Fig. 4-19)
  - Hair: **hypotrichosis** with thin, light hair; eyelashes absent
  - Skin: soft/smooth, thin wrinkled skin; **darkening of skin under eyes**; mild onychodystrophy
  - Teeth: dentition delayed; may have **peg-shaped, conical or missing teeth**
  - Eccrine glands: **risk for hyperthermia** as a result of ↓perspiration; ↓lacrimation may be seen
  - May develop chronic sinus disease, pulmonary infections, and asthma
- Boards Factoid: **hypohidrotic ectodermal dysplasia with immunodeficiency** is a result of mutations in *IKBKG/NEMO* (XLR) or *NFKBIA* (AD); susceptible to recurrent pyogenic or atypical mycobacterial infections

### Hidrotic ectodermal dysplasia (Clouston syndrome)

- AD mutation in *GJB6* (connexin 30)
- Clinical triad: **marked onychodystrophy**, **palmoplantar keratoderma**, and **hair abnormalities**
  - Onychodystrophy with variably hyperkeratotic/thin/striated/dyscolored nails; **hypotrichosis with thin/brittle hair**
  - Normal sweating, facial features, and teeth
  - Possible ophthalmologic (e.g., conjunctivitis, strabismus, and cataracts) and musculoskeletal (**tufted distal phalanges**) anomalies

### Ectodermal dysplasias due to *p63* mutation

- AD mutation in *p63* (critical transcription factor required for ectodermal, orofacial, and limb development)
- Overlapping features of clinical disease from *p63* mutations (thought to be a disease spectrum)
- Defined clinical syndromes include:
  - **Rapp-Hodgkin syndrome**: clefting of lip/palate/uvula, hypoplasia of maxilla, small narrow nails, and small conical teeth
  - **Ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC)** (**Hay-Wells syndrome**: congenital fusion of eyelids (**ankyloblepharon**) a/w facial clefting or mid-face hypoplasia; diffuse collodion-like peeling/erythema seen at birth; **scalp w/ chronic erosive dermatitis** → frequent *Staphylococcus* infections
  - **Ectrodactyly ectodermal dysplasia-cleft lip/palate syndrome (EEC)**: **ectrodactyly** (developmental anomaly of median ray of feet > hands → “**lobster claw**” deformity/missing digits), facial clefting, mild PPK, **conductive hearing loss**, and **genitourinary anomalies**
  - *p63* mutations also underlie acro-dermato-ungual-lacrima-tooth (ADULT) syndrome, limb-mammary syndrome (LMS), and split hand-foot malformation (SHFM)
- All syndromes may have wiry/sparse hair, dystrophic nails, ↓number of teeth/hypoplastic enamel, hypohidrosis, ↓tearing, and short stature or poor weight gain

### Rubinstein-Taybi syndrome

- Sporadic mutation in *CREBBP*
- Broad thumbs/halluces w/ racquet nails (**brachyonychia**)
- Capillary malformations, short stature, severe **mental retardation**, cryptorchidism, **congenital heart defects**, and typical facies (beaked nose, downslanting palpebral fissures, low-set ears, epicanthal folds, and grinning smile), **multiple pilomatricomas**

Other nail changes discussed in General Dermatology Chapter. Menkes disease, Bjornstad syndrome, Crandall syndrome, argininosuccinic aciduria, and citrullinemia are discussed in the General Dermatology Chapter. See [Table 4-12](#) and [Figs 4-20](#) and [4-21](#) for selected pediatric hair disorders.

## 4.8 INHERITED METABOLIC AND NUTRITIONAL DISORDERS

### Acrodermatitis Enteropathica (genetic form)

- Primary form is AR – mutations in *SLC39A4* (encodes intestinal zinc-specific transporter ZIP4)
  - Acquired/Secondary zinc deficiency (acrodermatitis-like syndrome): similar clinical findings and histology,

**Table 4-12.** Selected Pediatric Hair Disorders

Disorder	Pathogenesis	Clinical Features of Alopecia	Additional Clinical Features	Microscopy/Trichoscopy
Temporal triangular alopecia	Unknown	May be present at birth Usually diagnosed between 2–9 years of age Localized triangular patched of alopecia involving the <b>frontotemporal scalp</b> Often unilateral (left > right)	If large areas of involvement, consider cerebellotrigeminal dermal dysplasia	Trichoscopy and microscopy: <b>↓terminal hairs and ↑vellus hairs</b>
Atrichia with papules	Mutations in <b>hairless (HR)</b> gene	<b>Hair is normal at birth, then is quickly shed</b> after birth Follicular cysts and <b>milium-like papules</b> appear later	May be associated with vitamin D-resistant rickets (early-onset rickets, hypocalcemia, 2° hyperparathyroidism, and ↑1,25-OH vitamin D3)	Disintegration of the lower 2/3 of the hair follicle Multiple small cystic structures
Woolly hair	Nonsyndromic forms may be AD or AR Syndromic forms are AR	Poor hair growth noted from birth Hair is fine, dry, and curly with a corrugated appearance	<u>Naxos syndrome</u> : PPK, woolly hair, and <b>right</b> ventricular dysplasia/cardiomyopathy <u>Carvajal syndrome</u> : PPK, woolly hair, and <b>left</b> -sided cardiomyopathy	NA
Uncombable hair (pili trianguli et canaliculi)	Unknown	Presents during infancy or early childhood Hair is pale/blonde, dry, and unruly w/ <b>shiny</b> /"spun glass" appearance	Mild onychodystrophy Various ectodermal dysplasias	Light microscopy or scanning EM of hair: in cross section, hair shaft appears <b>triangular or reniform with a canalicular longitudinal depression</b>
Monilethrix	Mutations in hair keratins (e.g., <b>KRT81, KRT83, and KRT86</b> ) and desmoglein 4 ( <b>DSG4</b> ) Mutations in hair keratins are AD but mutation in DSG4 is AR	Hair typically appears normal at birth During infancy, hair becomes <b>short and brittle</b> with a <b>beaded appearance</b>	Koilonychia <b>Keratosis pilaris</b> (most common association)	Light microscopy/trichoscopy of hair: <b>uniform elliptical nodes along hair shaft</b>
Pili torti	Depending on associated syndromes	Hair typically sparse or absent at birth Poor hair growth Hair appears spangled	<b>Menkes kinky hair syndrome</b> <b>Bazex-Dupre-Christol syndrome</b> <b>Rombo syndrome</b> <b>Björnstad syndrome</b> <b>Crandall syndrome</b>	Light microscopy/trichoscopy of hair: <b>flattened, twisted hair shafts occurring at irregular intervals</b>
Trichorrhexis nodosa (Fig. 4-20)	Most commonly acquired as a result of trauma, such as from chemical and thermal treatments AD form also exists	<b>Most common hair shaft anomaly</b> Variably dry, lusterless, sparse hair Inherited form presents in infancy Acquired form presents in adolescence	Argininosuccinic aciduria Citrullinemia Oculo-dental-digital dysplasia Trichothiodystrophy Netherton syndrome	Light microscopy/trichoscopy of hair: intermittent <b>nodules with the appearance of broom bristles</b>
Trichorrhexis invaginata ("bamboo hair") (Fig. 4-21)	AR mutation in <b>SPINK5</b> (encodes LEKT1)	Dry, lusterless, sparse hair Poor hair growth	Marker for <b>Netherton syndrome</b>	Light microscopy/trichoscopy of hair: hair shaft intussuscepts into itself, creating the appearance of a <b>"golf tee"</b> or "ball in cup" joint seen
Marie Unna hypotrichosis	AD mutations in <b>U2HR</b>	Absence of scalp hair, eyebrows, and eyelashes at birth Hair grows in coarse and twisted Beginning in adolescence, hair is progressively lost	Widely spaced central incisors	Histology: mild-moderate inflammation, w/ ↓# of hair follicles, and without scarring or fibrosis Scanning EM: longitudinal grooves and peeling of the cuticle Light microscopy of hair: hair shafts have variable diameter and a twisted, bent appearance

Continued

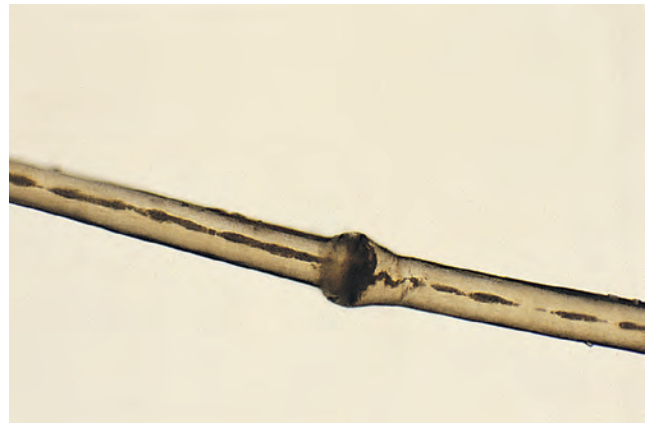


**Table 4-12.** Selected Pediatric Hair Disorders—cont'd

Disorder	Pathogenesis	Clinical Features of Alopecia	Additional Clinical Features	Microscopy/Trichoscopy
Alopecia mucinosa (follicular mucinosis)	In children, usually an <b>idiopathic</b> inflammatory dermatosis  <b>In children, rarely a presentation of cutaneous T-cell lymphoma</b>	Favors <b>head</b> , neck, and upper torso in children; may involve scalp or eyebrows  <b>Usually solitary</b> Presentation may include grouped follicular papules, with or without erythema, and scaling, which may coalesce into a boggy plaque Alopecia is a prominent feature	NA	Follicular degeneration Accumulation of mucin within hair follicles Periappendageal, perivascular, and/or interstitial lymphocytic/mixed inflammatory cell infiltrate If histologic features suggest mycosis fungoides, check <b>T-cell receptor gene rearrangement assay</b> from a skin biopsy
Loose anagen syndrome	Typically sporadic AD inheritance may be seen Defective anchoring of the hair shaft ( <b>defective inner root sheath keratinization</b> ) to the follicle resulting in <b>easily and painlessly plucked hair</b>	<b>Common in young, fair-haired girls 2–6 years of age</b> Diffuse hair thinning Hair may appear fine, limp, and matted Girls typically grow out of this without any intervention	Noonan-like syndrome cause by <i>SHOC2</i> mutations	Trichoscopy: <b>multiple anagen hairs with ruffled cuticles</b> and misshapen bulbs ("hockey stick")
Short anagen syndrome	Shortened anagen growth phase	Fine, short hair present at birth Poor hair growth	NA	Histology and trichogram: ↑telogen hairs
Nevoid hypertrichosis	Unknown	Localized patches of terminal hair of abnormal length, color, and/or diameter Common sites include lumbosacral area, anterior neck, and elbows ( <b>hypertrichosis cubiti</b> )	Rare associations with neurodevelopmental abnormalities	NA
Congenital hypertrichosis, generalized	Unknown; XLD inheritance has been reported, with both syndromic and nonsyndromic presentations	Universal overgrowth of terminal hair	Ambras syndrome: excessive vellus-like hairs on the face, ears, and shoulders; associated with mutations in tricho-rhino-phalangeal syndrome gene <i>TRPS1</i> Hypertrichosis lanuginosa: persistence of generalized lanugo hairs Hypertrichosis and gingival hyperplasia: diffuse overgrowth of terminal hair, gingival hyperplasia <b>Cornelia de Lange syndrome:</b> AD mutation in <i>NIPBL</i> in some cases; hirsutism, <b>synophrys</b> , <b>trichomegaly</b> , low hairline, mental/ psychomotor retardation, hypertonicity, short stature, fifth finger clinodactyly, simian crease, cryptorchidism, hypospadias, renal issues, congenital heart defects, and recurrent lung infections/ aspiration → death or hearing loss	NA
Keratosis pilaris	Abnormal keratinization of hair follicles	Affects 25%–60% of adolescents and adults Multiple small, scaling, and skin-colored to pink follicular papules Favor the <b>cheeks, upper arms, thighs, and buttocks</b>	Often associated w/ <b>atopy</b> , xerosis, or ichthyosis vulgaris Trisomy 21 Some ectodermal dysplasias	Histology: keratotic plugging of the pilosebaceous follicles; mild hypogranulosis and hyperkeratosis
Keratosis pilaris atrophicans, atrophoderma vermiculatum subtype	Usually sporadic; AD inheritance reported	Erythematous papules with follicular plugging, horn cysts, and <b>atrophic cribriform scarring</b> <b>Cheeks</b> and forehead; less commonly neck and extremities Typically presents between 5–12 yo	Trisomy 21 <b>Rombo syndrome</b> (atrophoderma vermiculatum, basal cell carcinoma, milia, telangiectasias, acral erythema)	Histology: epidermal atrophy; atrophic hair follicles with keratotic follicular plugs and dermal cysts; variable perifollicular inflammation

**Table 4-12.** Selected Pediatric Hair Disorders—cont'd

Disorder	Pathogenesis	Clinical Features of Alopecia	Additional Clinical Features	Microscopy/Trichoscopy
Keratosis pilaris atrophicans, ulerythema ophryogenes subtype	Usually sporadic; AD inheritance reported	Erythematous papules with <b>follicular plugging and atrophic scarring</b> Scarring alopecia of <b>eyebrows</b> Eyebrows, cheeks, and scalp; less commonly extremities Boys > girls; presents during infancy	Cardio-facio-cutaneous syndrome Noonan syndrome Cornelia de Lange syndrome Rubenstein-Taybi syndrome Wooly hair	Histology: keratotic plugging of pilosebaceous follicles and mild perifollicular inflammation (early) Dermal fibrosis and atrophy of the hair follicles and sebaceous glands (late)
Keratosis pilaris atrophicans, keratosis follicularis spinulosa decalvans subtype	XLR mutations in spermidine/spermine N(1)-acetyltransferase (SSAT) Mutations in membrane-bound transcription factor protease site 2 reported AD inheritance also described	Pink hyperkeratotic papules with follicular plugging Progressive scarring alopecia Eyebrows, eyelashes, and scalp Extensive keratosis pilaris begins in early childhood Scarring alopecia begins in adolescence	Palmoplantar keratoderma Corneal dystrophy with photophobia Atopic disease	Histology: concentric perifollicular fibrosis w/ mixed perifollicular inflammation and follicular plugging
Eruptive vellus hair cysts	Unknown, but may represent developmental anomaly of vellus hair follicles Often sporadic AD reported	1- to 3-mm skin-colored to <b>hyperpigmented</b> follicular papules Seen in school-aged children and adolescents Favor the <b>mid chest</b> , but may also be seen on the face, neck, extremities, buttocks, back, and abdomen	Hidrotic ectodermal dysplasia Hypohidrotic ectodermal dysplasia Pachyonychia congenita	Histology: cystic dilation of the infundibulum; cysts contain vellus hairs and laminated keratinaceous debris

**Figure 4-20.** Trichorrhexis nodosa. Light microscopic appearance. (From Eichenfield LF, et al. Neonatal and Infant Dermatology, 3rd Ed. Elsevier. 2015)**Figure 4-21.** Trichorrhexis invaginata in Netherton syndrome. Light microscopic appearance. (From Eichenfield LF, et al. Neonatal and Infant Dermatology, 3rd Ed. Elsevier. 2015)

but due to low zinc intake (alcoholics, anorexia) or malabsorption (IBD); also may arise in preterm or full-term infants who breastfeed from a **mother who has a low serum/breastmilk zinc level** or **premature infants** (have lower baseline zinc stores; risk highest when weaned off breastmilk)

- Greater zinc absorption occurs from breast milk as opposed to formula; presentation of primary acrodermatitis enteropathica may be delayed until weaning from breast milk to formula
- Triad of erosive vesiculopustular eczematous lesions involving the diaper area, face (periorificial),

and acral areas, along with **diarrhea** and **alopecia** (Fig. 4-22)

- Severe irritability, failure to thrive, photophobia, stomatitis/glossitis/perlèche, and nail dystrophy commonly seen
- On histology, **cytoplasmic pallor of keratinocytes in upper epidermis**, with ballooning and reticular degeneration; necrosis of keratinocytes in early lesions
  - Later lesions w/ confluent parakeratosis overlying psoriasiform epidermal hyperplasia w/o epidermal pallor



**Figure 4-22.** Zinc deficiency. Clinical photographs of a female infant with acrodermatitis enteropathica illustrating erosion, desquamation, and crusting in perioral region (A) and diaper area and acral surfaces (B). Photographs courtesy of Dr Angela Hernández-Martín, Madrid, Spain. (From Michael D. Corbo, Journal of the American Academy of Dermatology, Volume 69, Issue 4. Elsevier. 2013.)

- On laboratory, ↓serum zinc (<70 µg/dL), ↓serum alkaline phosphatase (zinc-dependent enzyme)
- Treatment: life-long zinc sulfate supplementation → fast resolution

### Biotinidase deficiency and multiple carboxylase deficiency

- Biotin is required for the function of four carboxylase enzymes (pyruvate carboxylase, propionyl-CoA-carboxylase, alpha-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase); in biotinidase deficiency and multiple carboxylase deficiency, loss of function of these enzymes results in disruption of fatty acid oxidation and accumulation of toxic metabolites
- **Biotinidase (BTD) deficiency:** AR disorder caused by mutations in *BTD* gene
- **Holocarboxylase synthetase (HLCS) deficiency:** AR disorder caused by mutations in the *HLCS* gene (→ loss of biotinidase function), more severe (**fatal** if untreated)
  - BTD deficiency presents in childhood whereas HLCS deficiency presents in early infancy
- Dermatologic manifestations: perioral/generalized dermatitis and alopecia

- Extracutaneous manifestations: seizures, developmental delay, hypotonia/ataxia, respiratory issues, vomiting (HLCS deficiency), diarrhea, metabolic ketoacidosis, hepatosplenomegaly, sensorineural hearing loss, conjunctivitis and **optic atrophy** (BTD deficiency), and organic aciduria
- Treatment = **IV biotin** replacement (HLCS deficiency requires ↑doses)

### Hartnup disease

- AR disorder caused by **mutations in *SLC6A19*** (encodes B(0)AT1, the intestinal and renal **neutral amino acid transporter**)
  - Symptoms result from inadequate absorption of tryptophan from the GI tract and failure of reabsorption of amino acids from the renal tubules
  - ↓tryptophan → ↓nicotinic acid and **pellagra-like symptoms** (e.g., photosensitivity)
- Cutaneous eruption presents in **childhood as an acute photodermatitis with erythema, blistering, scaling, crusting, and scarring occurring after sun exposure in sun-exposed areas of the face, neck, arms, dorsal hands, wrists, and lower legs**
  - Atrophic glossitis, angular stomatitis, vulvovaginitis, hair loss/fragility, and longitudinal nail streaks
- Untreated patients may develop cerebellar ataxia, seizures, intellectual disability, and emotional lability/psychosis
- Treatment: avoid sunlight; oral nicotinamide supplementation

### Phenylketonuria

- AR disorder 2° to loss of function mutation in **phenylalanine hydroxylase (*PAH* gene)** → inability to convert phenylalanine to tryptophan
- Cutaneous features: **diffuse hypopigmentation** with blonde hair and blue eyes, **eczematous dermatitis**, **photosensitivity**, and **sclerodermatous changes** of the torso and thighs
  - **Hypopigmentation** of skin/hair 2° to inhibitory effect of ↑phenylalanine on tyrosinase
  - **Mousy odor of urine**, short stature, and microcephaly
- **Mental retardation**, seizures, irritability, limb posturing and purposeless movements, psychosis, hyperactivity, and autistic features may develop if untreated
- Neonatal screening for PKU is included in the newborn screen in all states
- **Treatment with low phenylalanine diet/formula** under the guidance of a nutritionist → good prognosis; **AVOID aspartame**

### Homocystinuria

- AR disorder → deficiency of **cystathionine beta-synthetase (*CBS* gene)**, which catalyzes the formation of cystathionine from homocysteine and serine; thus deficiency → ↑homocysteine
- Cutaneous manifestations: hypopigmentation of skin and hair, brittle hair, malar erythema, **livedo reticularis**, and leg ulcers

- Other findings: myopia, **ectopia lentis** (downward displacement of lens), glaucoma, seizures, **mental retardation**, **marfanoid habitus**, **mitral valve prolapse**, generalized osteoporosis, platyspondylia (congenital flattening of the vertebral bodies), kyphoscoliosis, pectus carinatum, pectus excavatum, arachnodactyly, and **cardiovascular and cerebrovascular events** (e.g., thromboembolic events, pulmonary embolism, myocardial infarction, TIA, cerebrovascular accidents, abdominal aortic aneurysm, and **venous thrombosis**)
- Amino acid chromatography of the serum and urine: ↑urinary homocysteine and methionine; ↑serum cysteine and methionine + ↓homocysteine
- 50% of patients respond to vitamin B6 (+ folic acid and vitamin B12)
  - Otherwise, methionine-restricted, cysteine-supplemented diet

### Lesch-Nyhan syndrome

- **XLR disorder** 2° to hypoxanthine-guanine phosphoribosyl transferase mutation (*HGPRT* gene) → ↑uric acid, ↓dopamine
- **Orange uric acid crystals in the diaper** or hematuria may be seen in the first few months of life
- Neurodevelopmental delays, spastic cerebral palsy, choreoathetosis, and **intellectual impairment**
- **Significant self-mutilation** is characteristic
- Short stature/growth retardation, **uric acid nephropathy**, gout, and megaloblastic anemia
- Treatment of choice = allopurinol (100–300 mg/day) in divided doses; other hypouricemic agents may be considered
- Renal failure → morbidity and mortality

### Prolidase deficiency

- AR disorder 2° to mutations in **peptidase D** (*PEPD*) (encodes prolidase, a ubiquitous metalloenzyme involved in the catabolism of proteins)
- Cutaneous manifestations: **severe, progressive ulceration of lower extremities**, diffuse telangiectasias, photosensitivity, impetigo-like dermatitis, and an eczematous dermatitis
  - Leg ulcers are chronic and recalcitrant to therapy
  - **Recurrent infections** contribute to morbidity and mortality
- Other findings: intellectual impairment, neonatal hyperbilirubinemia, hepatosplenomegaly, and abnormal facies with **hypertelorism**/ptosis/beaked nose/frontal bossing

### Alagille syndrome

- AD mutation in Jagged 1 (*JAG1*) (encodes ligand for Notch receptor; pathway plays role in determining cell fates in early development)
- Typical triangular facies, w/ broad forehead, hypertelorism, deep-set eyes, large ears, sharply pointed chin

- **Tuberous xanthomas**, hypercholesterolemia, and hypertriglyceridemia
  - High serum cholesterol (>200 mg/dL) and triglyceride (500–2000 mg/dL) levels
- **Congenital intrahepatic biliary hypoplasia** (cholestasis, pruritus, and failure to thrive), posterior embryotoxon and retinal pigmentary changes, pancreatic insufficiency, renal and skeletal anomalies, congenital heart disease, and cerebrovascular events
- Treatment: liver transplantation is treatment of choice; pharmacologic management of hyperlipidemia → resolution of cutaneous xanthomas
  - Without treatment, death before 5 years of age

### Hunter syndrome

- **XLR disorder** 2° to mutation in *IDS* gene (encodes the lysosomal enzyme iduronate 2-sulfatase → accumulation of glycosaminoglycans in almost all organs and tissues)
- Cutaneous features: hypertrichosis, coarse facies (thick nose, thick lips, and tongue), **pebbled ivory-colored plaques between scapulae on upper back**, as well as the upper arms/thighs
- Cardiomyopathy, hepatosplenomegaly, skeletal deformities, macrocephaly, short stature, progressive neurodegeneration, hearing loss, papilledema, retinal pigmentation, and hoarse voice
- On histology, metachromatic granules in the cytoplasm of fibroblasts and sometimes in eccrine sweat glands; extracellular mucin in the mid and lower dermis
- ↑urinary heparin sulfate and dermatan sulfate (chondroitin sulfate B)
- Part of a family of disorders termed mucopolysaccharidoses – **Hurler syndrome** has dermal melanosis, mental retardation and “gargoyle” appearance; **all mucopolysaccharidoses have hypertrichosis and coarse facies**

### Alkaptonuria

- AR disorder 2° to mutation in **homogentisic 1,2-dioxygenase** (*HGO*) gene
- **Blue-gray pigmentation** (ochronosis) on face, nose, ears (seen well on cartilage), and sclera
- Dark sweat, cerumen, and urine (pH >7.0; adding NaOH to urine → darkening)
- Mitral/aortic valvulitis w/ ↑MI risk
- Intervertebral disc calcification; **severe arthritis**

## 4.9 INHERITED CONNECTIVE TISSUE DISORDERS

### Cutis laxa/generalized elastolysis

- AD forms (less common): **elastin gene** (*ELN*) or **fibulin 5** (*FBLN5*) mutations → dysregulation of elastic fiber network in the **skin** mainly (internal involvement uncommon); presents in early adulthood





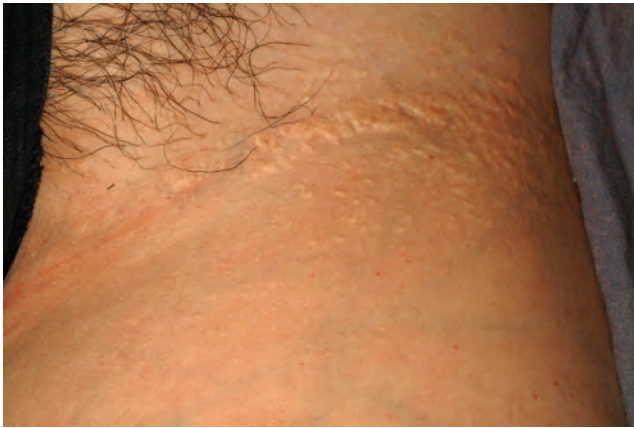
Figure 4-23. Cutis laxa. (Personal collection, Dr. Helen Shin)

- AR forms (**most common**): *FBLN5*, *EFEMP2/FBLN4*, *LTBP4*, *ATPase*, *ATP6V0A2*, *PYCR1*, and *ALDH18A1*; presents at birth to early childhood; **skin + severe internal involvement**
- XLR form (**occipital horn syndrome**, previously EDS IX): mutations in *ATPase*, Cu(2+)-transporting, alpha polypeptide (*ATP7A*) (allelic to Menkes disease)
- “Aged” facial appearance (**hound-dog facies**) with down-slanting palpebral fissures and a long philtrum (Fig. 4-23)
- Loose, **sagging skin** with reduced elasticity and resilience; deep voice 2° to vocal cord laxity
- Histology: sparse and/or fragmented elastic fibers
- AD cutis laxa
  - Primarily generalized cutaneous findings, cardiac valve abnormalities, aortic dilatation (variable), emphysema (uncommon), and hernias
- AR cutis laxa (ARCL)
  - **ARCL type I**
    - *FBLN5*, *EFEMP2*, or *LTBP4* mutations
    - Potentially fatal involvement of lungs (**hypoplastic lungs and emphysema**)
    - Cardiovascular abnormalities (aortic tortuosity and aneurysms)
    - Inguinal/diaphragmatic/umbilical hernias
    - GI/genitourinary diverticula
    - Joint laxity, arachnodactyly, and fractures (variable)
  - **ARCL type II**
    - *ATP6V0A2* (type IIA) or *PYCR1* (type IIB) mutations
    - Craniofacial anomalies
    - Delayed growth and development
    - Cutaneous features may be primarily acral
    - Pachygyria (IIA) and absent corpus callosum (IIB)
    - Translucent skin (IIB)
    - Joint laxity

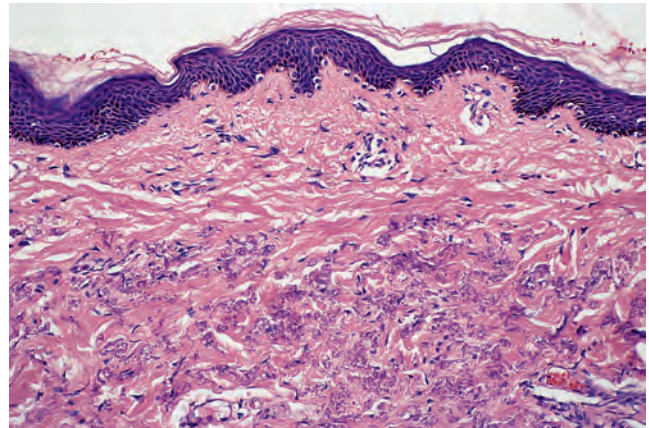
- Strabismus/myopia
- Improves with age
- **ARCL type III (De Barsy syndrome)**
  - *ALDH18A1* (type IIIA) or *PYCR1* (type IIIB) mutations
  - Developmental delay/dystonia/neurologic deterioration
  - Progeroid appearance
  - Reduced subcutaneous fat
  - Athetosis
  - Hyperammonemia (in some patients)
  - **Corneal clouding/cataracts**
- XLR cutis laxa (now termed Occipital Horn Syndrome)
  - Easy bruising and coarse hair (variable)
  - Tortuous arteries
  - Genitourinary diverticula
  - Inguinal, diaphragmatic and umbilical hernias
  - Long face w/ high forehead and hooked nose
  - **Wedge-shaped occipital calcifications** (occipital horns)
  - Hip dislocations (joint laxity)
- Acquired cutis laxa
  - Primarily adults w/ sagging of skin and little associated internal involvement
  - Cutaneous involvement may be primarily acral; generalized involvement typically begins on the face/neck
  - May occur in association with drugs (**penicillamine** and **isoniazid**), other cutaneous disorders (e.g., cutaneous lymphoma, Sweet syndrome-like eruption, interstitial granulomatous dermatitis, and cutaneous mastocytosis) or **systemic disease** (rheumatoid arthritis, sarcoidosis, SLE, and infectious disorders)

## Pseudoxanthoma elasticum

- AR disorder as a result of mutations in *ABCC6* (ATP-binding cassette, subfamily C, member 6) gene → 2° mineralization of the elastic tissue of the eyes, skin, and arteries
- Presents during childhood or 2nd/3rd decade of life
- Cutaneous manifestations
  - **Thin, yellowish papules in flexural areas** arise during first or second decade of life (Fig. 4-24)
    - Typically first appear on the lateral aspects of the neck
    - Papules coalesce to form cobblestone-like plaques resembling “**plucked chicken skin**”
    - Antecubital and popliteal fossae, wrists, axillae, groin, and periumbilical area (in multiparous women) are involved
    - **Perforating PXE**: in advanced disease, ↑dermal calcium deposition and extrusion of this yellowish material through the epidermis may occur
    - Loss of recoil and sagging skin in axillae and groin
    - Yellow papules may develop in oral/anogenital mucosa
- Ocular manifestations
  - **Asymptomatic angioid streaks (Bruch’s membrane rupture)** usually in first decade
    - “Owl’s eyes”: paired areas of hyperpigmented spots straddling an angioid streak



**Figure 4-24.** Pseudoxanthoma elasticum. (From Lebwohl MG, et al. Treatment of Skin Disease: Comprehensive Therapeutic Strategies, 4th ed. Elsevier. 2013)

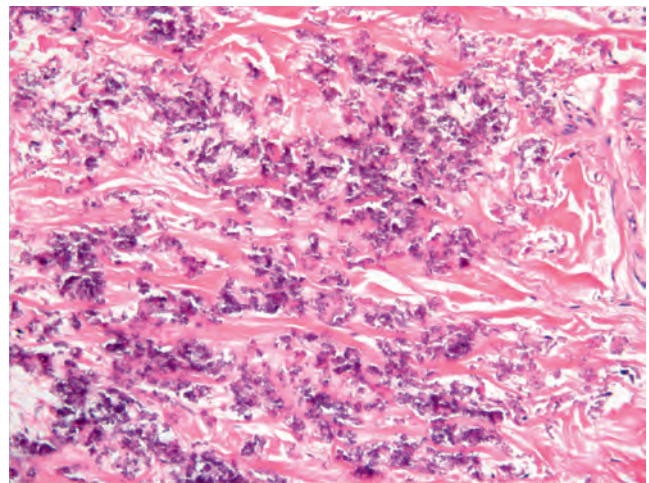


**Figure 4-25.** Pseudoxanthoma elasticum. Note the short, curled elastic fibers in the reticular dermis. (From Weedon D. Weedon's Skin Pathology, 3rd ed. Elsevier. 2009)

- Agioid streaks also seen in **Paget's disease of bone, sickle cell anemia, thalassemia, EDS, lead poisoning,** and age-related degeneration
- Macular degeneration, optic drusen, and retinal hemorrhage (→ blindness)
- Mottling of retinal pigment epithelium
  - Most prevalent ophthalmologic finding; may precede development of angioid streaks
- Cardiovascular manifestations
  - Intermittent claudication, loss of peripheral pulses, renovascular **hypertension, mitral valve prolapse, angina/myocardial infarction,** and **stroke**
  - Progressive calcification of elastic media and intima → atheromatous plaques involving predominantly medium-sized arteries (esp. in extremities)
- GI manifestations
  - **Gastric artery hemorrhage,** hematemesis, epistaxis
- Obstetric complications
  - ↑risk of **first trimester miscarriage** and maternal cardiovascular complications
- On histology, **distorted, basophilic, and fragmented calcified elastic fibers** in mid/deep reticular dermis (Fig. 4-25 and Fig. 4-26)
- Morbidity and mortality 2° to **GI hemorrhage, cerebral hemorrhage, atherosclerotic disease, and myocardial infarction**

### Osteogenesis imperfecta (OI)

- Mutations in **type I collagen** → fragile bones (poor cortical modeling and less trabecular bone formation)
- There are at least 8 well-defined types of OI, but Types I–IV account for 90%
  - Types I (**most common form**, accounts for 50% of OI; generally **mild**; fractures in childhood and adolescence), II (**most severe form, fatal** in perinatal period), III (progressive and deforming), and IV
    - **AD inheritance**; due to mutations in type I collagen genes **COL1A1 and COL1A2**
  - Onset (birth to adulthood) and severity depend on type



**Figure 4-26.** Pseudoxanthoma elasticum. Note the short, curled elastic fibers in the reticular dermis. They are basophilic. (From Weedon D. Weedon's Skin Pathology, 3rd ed. Elsevier. 2009)

- Cutaneous manifestations
  - Thin, atrophic, and **translucent skin**
  - **Easy bruisability**
  - Scars may be atrophic or hypertrophic
- Musculoskeletal manifestations
  - Hyperlaxity of ligaments and hypermobility of joints
  - **Brittle bones + fractures** (skull, long bones, and vertebrae; occurs *in utero* in severe forms)
  - **Scoliosis**
  - **Beaded ribs**
  - Limb deformities
- Other manifestations
  - **Blue sclerae are seen ~90% of patients**
  - Otosclerosis with **hearing loss** may begin during adolescence
  - Fragile/dicolored teeth
  - Dentinogenesis imperfecta (DI)

- Mitral and aortic valve prolapse/dilatation and regurgitation
- Cystic medionecrosis of the aorta
- Neurologic features include macrocephaly, hydrocephalus, syringomyelia, and basilar invagination
- Variable prognosis depending on disease type and severity:
  - Types I and IV: normal life span
  - Type II: **death in perinatal period**
  - Type III: increased mortality in 3rd/4th decade due to **respiratory failure** (secondary to kyphoscoliosis) or head trauma

## Ehlers-Danlos syndrome (EDS)

- Heterogeneous group characterized by abnormal collagen structure and/or function within the skin, joints, and vasculature (Table 4-13)
- Classical EDS (most common subtype)
  - May deliver/be delivered pre-term as a result of early rupture of fetal membranes; normal life span
  - Mucocutaneous manifestations
    - Velvety, soft, and doughy consistency of skin
    - **Marked hyperextensibility of skin**
    - **Poor wound healing** (“cigarette paper” scars)

**Table 4-13.** Ehlers-Danlos Syndrome Classification

Type	Genes	Inheritance	Skin Findings	Joint Changes	Other
Classical (formerly <b>Type I</b> , “gravis” and <b>Type II</b> , “mitis”)	<b>COL5A1</b> , <b>COL5A2</b>	AD	Hyperextensibility Easy bruising Fragile skin Widened atrophic (“fish mouth” or “cigarette paper”) scars <b>Molluscoid pseudotumors</b> (overlying extensor joints and pressure points) Spheroids	Hypermobility and joint dislocations	<b>(+)Gorlin’s sign</b> Absence of lingual frenulum
Hypermobility (formerly <b>Type III</b> )	<i>TNXB</i>	AD/AR	Mild	<b>Hypermobility</b> Chronic joint pain + arthritis Recurrent <b>dislocations and subluxations</b>	Deficiency of <b>tenascin X</b>
Vascular (formerly <b>Type IV</b> )	<b>COL3A1</b>	AD	Thin, translucent skin Extensive bruising Early varicosities (can <b>visualize veins under skin</b> easily) Acrogeria	Small joint hypermobility	Mnemonic: “IV = blood vessels” <b>Rupture of bowel, uterus, or arteries</b> Most <b>life-threatening</b> form
Kyphoscoliotic (formerly <b>Type VI</b> )	Lysyl hydroxylase 1 ( <i>PLOD1</i> )	AR	Mild	Hypermobility <b>Severe scoliosis</b>	Severe muscle hypotonia <b>Ruptured globe, blindness, retinal detachment, or keratoconus</b> Marfanoid Osteopenia Ascorbic acid supplementation may help
Arthrochalasic (formerly <b>Types VIIa and VIIb</b> )	<i>COL1A1</i> , <i>COL1A2</i>	AD	Mild	<b>Most severe hypermobility</b> with recurrent subluxations/dislocations (much more severe than Hypermobility type)	<b>Congenital hip dislocation</b> Short stature
Dermatosparaxis (formerly <b>Type VIIc</b> )	Procollagen N-proteinase ( <b>ADAMTS2</b> )	AR	Severe fragility <b>Sagging, redundant skin</b> , and bruising	Mild	Umbilical/inguinal hernias Premature rupture of fetal membranes
Periodontitis type (formerly <b>Type VIII</b> )	Unclear	AD	Hyperextensible skin with scarring (esp. pretibial) and bruising	Mild	<b>Severe periodontitis → teeth loss</b>

(Adapted from Paller S, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 4th Ed. Elsevier. 2011)



- Widened atrophic cutaneous scars (“fishmouth” wounds)
- Piezogenic pedal papules
- Fragile blood vessels → hematomas and **easy bruising**
- Subcutaneous spheroids (fat lobules that have **calcified** after losing their blood supply)
- Molluscoid **pseudotumors** associated with scars over knees and elbows
- **Blue sclerae**
- **Gorlin’s sign**: ability to touch tip of nose with tongue (50%)
- Musculoskeletal manifestations
  - Generalized joint hypermobility
  - **Double-jointed fingers**
  - **Frequent subluxation of larger joints**
  - Chronic joint and limb pain
  - **Kyphoscoliosis**
  - **Pes planus**
- GI manifestations
  - Hiatal/inguinal hernia, postoperative hernias, and anal prolapse
  - GI bleeding/rupture
- Cardiac manifestations
  - **Mitral valve prolapse**
  - Aortic root dilation
- Vascular EDS
  - **Life-threatening risk of blood vessel and organ rupture** → sudden death in third/fourth decade (arterial or colonic rupture; **maternal death may occur as a result of uterine or arterial rupture**)
  - Cutaneous manifestations
    - Easy bruising
    - **Thin and translucent skin with visible underlying blood vessels**
    - Skin is not hyperextensible, but can be fragile
    - Lack of subcutaneous fat
  - Facial features: thin, pinched nose; prominent sunken eyes; thin upper lip; and lobeless ears
  - **Blue sclera** (>90%)
  - Acrogeria
  - **Hypermobility limited to digits**
  - Congenital talipes (club foot)
  - Recurrent pneumothoraces
  - Arterial (including aorta) dissection, rupture, and aneurysm of medium-sized vessels
    - **Spontaneous rupture of arteries** (medium-sized) may occur during childhood, and incidence peaks during third and fourth decade
    - **Intestinal rupture is common** (sigmoid colon #1 site)
  - Intracranial aneurysms associated with cerebrovascular accidents
  - Obstetric complications, including uterine and arterial rupture, massive postpartum hemorrhage, and severe laceration from tearing at vaginal delivery
  - Short stature
- Hypermobile EDS
  - Not prone to life-threatening complications
  - **Severe joint laxity, recurrent dislocations/subluxations**, and chronic joint pain +/- arthritis

- Mitral valve prolapse
- Symptoms of autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS)
- GI and urinary symptoms

### Marfan syndrome (MFS)

- AD mutations in the *FBN1* gene (encodes **fibrillin-1**)
- Manifestations may not present until adolescence or in 30s–40s
- **Tall with long extremities** (marfanoid habitus)
  - Arm span is characteristically greater than height
  - After puberty, upper segment (vertex to pubis) to lower segment (pubis to sole) ratio is <0.86
- Lack of subcutaneous fat, presence of **striae** on upper chest, arms, thighs, and abdomen and increased risk of **elastosis perforans serpiginosa**
- Skeletal manifestations
  - **Arachnodactyly**
  - Kyphoscoliosis, pectus excavatum, and dolichocephaly
  - Pes planus
  - Joint laxity, patellar dislocation, and hip dislocation
- Ocular manifestations
  - **Ectopia lentis (upward lens displacement; 60% of patients)**
  - Ocular globe elongation leading to myopia (~40%)
  - Retinal detachment, cataracts, and glaucoma
- Cardiovascular manifestations (70%)
  - **Dilatation of ascending aorta → regurgitation, CHF, dissection/aneurysm, and rupture**
  - **Mitral valve prolapse**
  - Left ventricular dilation
  - Cardiac complications may → death
- Pulmonary manifestations
  - **Spontaneous pneumothorax**, apical blebs, and bullous emphysema

### Buschke-Ollendorf syndrome

- AD disorder due to mutation in *LEMD3/MAN1* (LEM domain-containing-3/MAN antigen 1) gene → ↑TGF-β signaling
- **Dermatofibrosis lenticularis disseminata** (collagen-type nevus) on buttocks, proximal trunk, and limbs
  - Symmetric, small, uniform, yellow to skin-colored dermal papules coalescing into plaques; onset in childhood (typically in 1st year of life)
- **Osteopoikilosis (“spotted bones”)**
  - **Asymptomatic circular densities** in carpal bones, tarsal bones, phalanges of hands and feet, pelvis, and **epiphyses and metaphyses of long bones**
  - Often noted incidentally on plain films (1- to 10-mm round opacities)
- Histology: abundant thickened collagen fibers and elastic fibers (often fragmented and clustered into nets)

### Infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF)

- Allelic autosomal recessive (AR) diseases caused by mutations in *ANTXR2/CMG2* gene (capillary



- morphogenesis protein-2) → abundance of hyalinized fibrous tissue in skin and internal organs
  - ISH presents within first 6 months of life with cutaneous, mucosal, skeletal, and internal organ involvement and **death in early childhood**
  - JHF presents during early childhood with cutaneous, mucosal, and skeletal/joint (often debilitating) involvement only; **survival into adulthood**
- Cutaneous manifestations
  - Thickened skin and hyperpigmentation overlying bony prominences is characteristic of ISH
  - Perianal nodules
  - **Small pearly papules** on ears and face (perinasal and perioral)
  - Scalp nodules are characteristic of JHF
- Oral manifestations
  - Thickening of oral mucosa
  - **Gingival hypertrophy**
  - Marked curvature of dental roots
  - Replacement of periodontal ligament by hyaline fibrous material
  - Feeding difficulty
- Musculoskeletal manifestations
  - **Debilitating joint contractures** and tumors
  - Osteolytic bone lesions are characteristic of JHF
- Normal intelligence
- Visceral involvement (ISH only): hyaline deposits develop in multiple internal organs w/ recurrent infections, malabsorption, protein-losing enteropathy, and failure to thrive
- Histology: ↑# of fibroblasts embedded in **hyalinized connective tissue stroma** that is homogeneous, amorphous, and acidophilic (PAS-positive)
- ISH has a poor prognosis with death by 2 years of age from **recurrent pulmonary infection and GI complications**
- In JHF, survival into adulthood (death often by 4th decade)

### Lipoid proteinosis (hyalinosis cutis et mucosae, Urbach-Wiethe disease)

- AR disorder due to mutations in the **extracellular matrix protein 1 (ECM1) gene**; ↑ in South Africa
- Thickening of basement membrane and deposition of hyaline material in dermis → characteristic thickening of the skin, mucous membranes, and certain viscera
- **Hoarse cry** or weak cry from infiltrated vocal cords is the **first clinical sign** (occurs in infancy and persists for life)
- Cutaneous lesions develop during first few 2 years of life in two overlapping stages
  - First stage: vesicles and hemorrhagic crusts involving the face, extremities, and oral mucosa develop in association with trauma and resolve with “ice-pick” scars
  - Second stage: ↑hyaline deposition within the dermis → yellow, waxy, and coalescing papules/nodules on the face/neck and extremities; **beaded eyelid papules resembling “string of pearls”** (50%); verrucous nodules on elbows/knees/hands

- Infiltration by yellow papules/plaques of mucosa of pharynx, soft palate, tonsils, and lips
- **Thickened “woody” tongue; inability to protrude tongue** (due to shortened frenulum)
- **Respiratory difficulty** a/w upper respiratory tract infections and may require tracheostomy; occasionally fatal in infancy (major cause of early death)
- Neurologic manifestations include **seizures** and neuropsychiatric symptoms, a/w pathognomonic sickle or “bean-shaped” calcifications in temporal lobes or hippocampus
- Histology: **deposition of amorphous or laminated basement membrane-like material containing collagen (types II and IV) and laminin** around blood vessels, dermal-epidermal junction, adnexal epithelia, and in connective tissues (appears as vertically oriented pink dermal deposits)
  - Deposits are PAS(+) and diastase-resistant

### Focal dermal hypoplasia (Goltz syndrome, Goltz-Gorlin syndrome)

- X-linked dominant (XLD) disorder due to mutations in the **PORCN** (porcupine) gene (regulator of Wnt signaling proteins, which are critical for embryonic development of skin, bone, teeth, and other structures)
- Majority of patients are heterozygous females (90%); **lethal in males**
- Cutaneous manifestations:
  - Widely distributed linear/Blaschkoid areas of **hypoplasia/atrophy** of the skin, with **telangiectasias** (Fig. 4-27)



**Figure 4-27.** Goltz syndrome (focal dermal hypoplasia). Linear streaks of dermal hypoplasia with visible telangiectasia in an affected boy. The condition is presumed to be lethal in males, suggesting that this boy's manifestation reflects post-zygotic mosaicism. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)

- Soft, yellow to reddish-yellow nodular outpouchings caused by herniation of subcutaneous fat through thinned dermis
- Dysmorphic facies (notched nasal ala and malformed ears)
- Large cutaneous ulcers (from a congenital absence of skin) that heal w/ atrophic scarring
- Streaky hyper- and/or hypopigmentation
- Red (“raspberry-like”) papillomas; favors lips, anogenital region, larynx and acral skin
- Hair is thin or absent
- Dystrophic or completely absent nails
- Skeletal manifestations
  - Oligodactyly, syndactyly, ectrodactyly (lobster claw deformity), and polydactyly
  - Microcrania, asymmetric development of skull, pointed mandible, and deviated nasal septum
  - Scoliosis, kyphosis, spina bifida occulta, rudimentary tail, and fusion of vertebral bodies
  - Osteopathia striata: vertical striations in long bone metaphyses on X-ray
- Ophthalmologic manifestations (40%)
  - Colobomas of iris/choroid/retina/optic disc
  - Strabismus
  - Anophthalmia, microphthalmia, and incomplete development of the retina and optic nerve
  - Hypopigmented/hyperpigmented retina, cloudy vitreous, and subluxation of lens
- Dental manifestations
  - Underdeveloped, dysplastic, or absent teeth
  - Delayed eruption of primary dentition
  - Notched incisors
  - Enamel hypoplasia
  - Severe malocclusion if mandible is malformed
- Intelligence usually normal, though severe mental impairment has been reported
- Histology: markedly decreased/absent dermis with herniated fat located abnormally close to epidermis
- FOCAL has been suggested as an acronym that incorporates the key clinical features of this disorder:
  - Female, XLD
  - Osteopathia striata
  - Colobomas
  - Aplasia ectoderm elements
  - Lobster claw deformity

### Congenital contractual arachnodactyly (Beals syndrome and distal arthrogryposis type 9)

- AD mutation in fibrillin 2 (*FBN2*) gene
- Crumpled ears, Marfanoid habitus, arachnodactyly, congenital contractures of small and large joints that usually improve over time, kyphoscoliosis, and pectus excavatum
- Characteristic facial features
  - High forehead
  - Down-slanting palpebral fissures
  - Hypertelorism

- Anteverted nostrils
- Low-set and abnormal auricles
- Retromicrognathia
- Short neck
- Cardiac manifestations: mitral valve prolapse and aortic root dilation

### Restrictive dermopathy (tight skin contracture syndrome)

- AR disorder as a result of mutations in lamin-A (*LMNA*) or zinc metalloproteinase STE24 (*ZMPSTE24*) → ↑prelamin A (accumulates in the nucleus → nuclear membrane toxicity)
- Prenatal manifestations
  - Intrauterine course characterized by fetal akinesia or hypokinesia deformation sequence
  - Polyhydramnios with reduced fetal movements noted beginning at about 31 weeks
  - Clavicular hypoplasia develops *in utero*
  - Birth typically occurs before 35 weeks of gestation as a result of PROM
- Cutaneous manifestations
  - Taut translucent, thin skin with erosions and fissures
  - Skin tears in response to stress of delivery, resuscitation, and neonatal movements
  - Complications include infection and dehydration after fluid loss
  - Increased transepidermal water loss leads to hypoalbuminemia and electrolyte imbalance
- Dysmorphic facies
  - Fixed round open mouth with micrognathia
  - Small pinched nose
  - Hypertelorism
  - Enlarged fontanelles
  - Widened cranial sutures
- Flexion contractures
- Restrictive pulmonary disease as a result of thoracic stiffness and severely restricted movements
- Death secondary to respiratory insufficiency shortly after birth

### Stiff Skin syndrome (congenital fascial dystrophy)

- AD disorder due to mutations in *FBN1* (fibrillin-1)
- Progressive development of stony-hard skin on thighs, buttocks, lower back, and shoulders
- Joint contractures (esp. large joints), scoliosis, tiptoe gait, narrow thorax in relation to arm girdle, restrictive pulmonary changes, growth retardation, and postural and thoracic wall irregularities
- On histology, fascial sclerosis; ↑fibroblast cellularity; thickened, sclerotic, horizontally oriented collagen bundles in deep reticular dermis and/or subcutaneous septa

## 4.10 AUTOINFLAMMATORY DISORDERS (PERIODIC FEVER SYNDROMES)

### Epidemiology

- Predominantly hereditary (rarely acquired) syndromes characterized by **recurrent, spontaneous, inflammatory episodes** w/ varying degrees of severity and duration; presenting w/ fever and variable cutaneous, serosal, mucosal, ocular, neurologic, and osteoarticular manifestations

### Pathogenesis

- Disorders of innate immunity caused by ↑production of proinflammatory cytokines (e.g., IFN- $\alpha$ , IFN- $\gamma$ , IL-6, IL-1, and TNF- $\alpha$ ) as a result of aberrant signaling of cell surface or intracellular innate immune receptors
- Cytokine receptors, receptor antagonists, and components of the **inflammasome** are involved and result in intracellular protein complexes that enable the **autocatalytic activation of inflammatory caspases, driving the release of proinflammatory cytokines**
- These innate immune cells are activated by endogenous or exogenous stimuli, so-called pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)

- Clinical features
  - Most patients present in infancy to early childhood; adult-onset reported for FMF and TRAPS
  - **Fever** = key feature of most of the autoinflammatory syndromes and is periodic in nature
  - Know the key clinical features for each syndrome (Table 4-14)

### Histopathology

- Histology (all except PAPA and Blau): moderate-dense dermal perivascular and interstitial neutrophils (“**neutrophilic urticarial dermatitis**”) +/- dermal edema

### Treatment

- The treatment of each autoinflammatory syndrome is disease-specific – agents such as **anakinra**, etanercept, and **canakinumab** are commonly used
- **Colchicine** is crucial in preventing amyloidosis in patients with FMF

### Prognosis/clinical course

- Untreated, many of the autoinflammatory syndromes → significant morbidity and mortality
- **DITRA, DIRA, and NOMID** may be fatal during infancy or childhood
- **Secondary AA amyloidosis** is a complication of FMF and the cryopyrin-associated periodic syndromes (CAPS)

**Table 4-14.** Features of Selected Autoinflammatory Syndromes

Diagnosis	Gene (Protein)	Inheritance	Clinical Features	Rx	Other comments
<b>Cryopyrin-associated periodic syndromes</b>					
Familial cold autoinflammatory syndrome	<b>CIAS-1/NLRP3</b> (cryopyrin)	AD	<u>Age of onset:</u> Infancy <u>Skin:</u> Cold-induced urticaria, favors extremities (> face, trunk) <u>Systemic:</u> Arthralgia, conjunctivitis	IL-1 antagonists	Short attacks (minutes- 3 days)
Muckle-Wells syndrome	<b>CIAS-1/NLRP3</b> (cryopyrin)	AD	<u>Age of onset:</u> Any <u>Skin:</u> Widespread urticaria <u>Systemic:</u> Abdominal pain, “ <b>lancing</b> ” extremity pain, conjunctivitis, optic disk edema, arthralgia/arthritis, and sensorineural <b>hearing loss</b>	<b>IL-1 antagonists</b>	Febrile attacks last 1-2 days High risk of <b>secondary AA amyloidosis</b> (25%)
NOMID/CINCA	<b>CIAS-1/NLRP3</b> (cryopyrin)	AD	<u>Age of onset:</u> Neonatal <u>Skin:</u> Widespread urticaria +/- oral ulcers; <b>dysmorphic facies</b> (frontal bossing and protuberant eyes) <u>Systemic:</u> <b>Deforming arthropathy</b> , arthritis, epiphyseal overgrowth, significant ocular involvement (may → <b>blindness</b> ), sensorineural hearing loss, lymphadenopathy, HSM, seizures, <b>aseptic meningitis</b>	IL-1 antagonists	<b>Febrile attacks occur continuously</b> Secondary AA amyloidosis <b>Significant morbidity/ mortality</b> in childhood (if untreated)

**Table 4-14.** Features of Selected Autoinflammatory Syndromes—cont'd

Diagnosis	Gene (Protein)	Inheritance	Clinical Features	Rx	Other comments
<b>Monogenic periodic fever syndromes</b>					
Hyper-IgD syndrome (Mevalonate kinase deficiency)	<b>MVK</b> (mevalonate kinase)	AR	<u>Age of onset:</u> Infancy <u>Skin:</u> Widespread polymorphous eruption (morbilliform or urticarial most commonly) <u>Systemic:</u> Arthralgia, abdominal pain, vomiting, diarrhea, arthritis, cervical LAN, HSM	IL-1 antagonists, TNF- $\alpha$ antagonists	Febrile attacks last up to 7 days $\uparrow$ Incidence in Dutch and Northern Europeans $\uparrow$ serum IgD and urinary mevalonate levels
TNF-receptor-associated periodic syndrome (TRAPS)	<b>TNFRSF1A</b> (TNF receptor superfamily 1A/p55 TNF receptor)	AD	<u>Age of onset:</u> Any <u>Skin:</u> <b>Painful migratory/serpiginous plaques</b> (often edematous) on extremities; may become ecchymotic <u>Systemic:</u> Serositis, periorbital edema, scrotal pain, <b>migratory myalgias</b> (underlying rash)	Corticosteroids, TNF- $\alpha$ antagonists	Febrile attacks often long (1-6 weeks) <b>Secondary AA amyloidosis</b> (15%) Labs: $\downarrow$ serum soluble TNF receptor levels
Familial Mediterranean fever (FMF)	<b>MEFV</b> (pyrin/marenostrin)	AR	<u>Age of onset:</u> Any <u>Skin:</u> <b>Erysipelas-like</b> rash, favors <b>legs/feet</b> <u>Systemic:</u> Serositis and arthritis	<b>Colchicine</b> , NSAIDs, IL-1 antagonists, and TNF- $\alpha$ antagonists	Febrile attacks last 1-3 days $\uparrow$ Incidence in Mediterranean populations <b>Secondary AA amyloidosis</b> (mainly in homozygotes; prevented by colchicine)
<b>Autoinflammatory pyogenic disorders</b>					
Pyogenic arthritis, pyoderma gangrenosum, acne syndrome (PAPA)	<b>PSTPIP1/CD2BP1</b> (Proline-serine-threonine phosphatase-interacting protein 1/CD2 antigen binding protein 1)	AD	<u>Age of onset:</u> Childhood <u>Skin:</u> Pyoderma gangrenosum and nodulocystic acne <u>Systemic:</u> <b>Sterile pyogenic oligoarthritis</b> , afebrile	TNF- $\alpha$ antagonists, IL-1 antagonists	
Deficiency of the IL-1 receptor antagonist (DIRA)	<b>IL1RN</b> (IL-1 receptor antagonist)	AR	<u>Age of onset:</u> Neonatal <u>Skin:</u> Neutrophilic pustular dermatosis, ichthyosis <u>Systemic:</u> Sterile multifocal osteomyelitis, periostitis, afebrile	<b>IL-1 antagonists</b>	
Generalized pustular psoriasis/Deficiency of the IL-36 receptor antagonist (DITRA)	<b>IL36RN</b> (IL-36 receptor antagonist)	AR	<u>Age of onset:</u> Infancy, childhood <u>Skin:</u> <b>Generalized pustular psoriasis</b> <u>Systemic:</u> Malaise, multiorgan failure	NSAIDs, Vitamin D analogs, systemic retinoids, TNF- $\alpha$ inhibitors, IL-1 inhibitors	Multiorgan failure
<b>Autoinflammatory granulomatous disorders</b>					
Blau syndrome/early-sarcoidosis	<b>NOD2/CARD15</b> (nucleotide-binding oligomerization domain 2/caspase recruitment domain 15)	AD, sporadic	<u>Age of onset:</u> Childhood <u>Skin:</u> Sarcoidal granulomatous dermatitis, ichthyosiform dermatitis <u>Systemic:</u> Fever (30%), polyarticular arthritis (favors hands/feet), synovitis and tenosynovitis	Corticosteroids, IL-1 antagonists, TNF- $\alpha$ antagonists,	

## 4.11 NEUROCUTANEOUS SYNDROMES

### Neurofibromatosis (NF)

- Encompasses three distinct disorders (NF1, NF2, and schwannomatosis), characterized by  $\uparrow$ propensity toward tumor development, particularly of the nerve sheath
  - 90% of cases are NF1
- NF1 (von Recklinghausen's disease)

- AD disorder caused by mutations in **neurofibromin (NF1)**, a tumor suppressor gene
  - Neurofibromin is a cytoplasmic protein that **negatively regulates Ras activation**
  - 50% are sporadic mutations and mosaic/segmental disease can occur
- Diagnostic criteria for NF-1 ([Box 4-1](#))
- Manifestations by age of presentation listed in [Table 4-15](#)



# Box 4-1. Diagnostic Criteria for NF1

## Must have >2 of the following:

Six café-au-lait macules  $\geq 0.5$  cm prepubertal or  $\geq 1.5$  cm postpubertal  
 Intertriginous freckling  
 Plexiform neurofibroma or >2 dermal neurofibromas  
 >2 Lisch nodules  
 Optic nerve glioma  
 Pathogenomic skeletal dysplasia (tibial or sphenoid wing dysplasia)  
 Affected first-degree relative

**Table 4-15.** Manifestations of NF1 by Age of Presentation

Average Age of Onset	Cutaneous	Ocular	Neurologic	Skeletal
Infancy to early childhood	Café-au-lait macules Plexiform neurofibromas		Learning disabilities Attention deficit disorder Autism Macrocephaly	Tibial dysplasia Sphenoid wing dysplasia
Prepubertal	Intertriginous freckling (Fig. 4-28)	Optic gliomas	Brainstem gliomas Meningiomas	Scoliosis
Adolescence	Dermal or subcutaneous neurofibromas	Lisch nodules		
Adulthood	Malignant peripheral nerve sheath tumors			

- Cutaneous manifestations:
  - **Neurofibroma**: soft papule that invaginates upon finger pressure (“buttonholing”)
  - Plexiform neurofibroma: overlying CALM and/or hypertrichosis; “bag of worms” texture (seen in ~25% of patients)
  - **Malignant peripheral nerve sheath tumor (MPNST)**: rapid enlargement or pain of plexiform neurofibroma (**10% risk**)
  - **CALM** (typically  $\geq 6$ ,  $\uparrow$ #/size in first 5 years)
  - Axillary freckling (**Crowe’s sign**)
- Ocular manifestations
  - **Lisch nodules** (>90% of patients by 10 years of age)
  - Choroid nevus and glaucoma
- Skeletal manifestations
  - **Sphenoid wing dysplasia**: pulsating exophthalmos may be noted, though often asymptomatic
  - Macrocephaly
  - Scoliosis
  - **Congenital tibial pseudarthroses (tibial)**
  - Additional skeletal abnormalities: thoracic cage asymmetry, osteoporosis, and pathologic fractures
  - Short stature
- Neurologic manifestations:
  - Learning disability, ADHD, and autism
  - Seizures
  - Hydrocephalus
  - **Optic glioma** (can  $\rightarrow$  blindness; seen w/ precocious puberty), astrocytomas, meningiomas, vestibular/acoustic schwannoma/neuroma, and ependymoma



**Figure 4-28.** von Recklinghausen’s neurofibromatosis. **(A)** Café-au-lait spots vary in size and have a smooth border. **(B)** Axillary freckling (Crowe’s sign) is a pathognomonic sign. (From Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 6e. Elsevier. 2015)

- Other manifestations:
  - Other tumors: neurofibrosarcoma, rhabdomyosarcoma, **pheochromocytoma**, Wilms' tumor, and **chronic myelogenous leukemia**
  - Hypertension may develop as a result of a pheochromocytoma or renal vascular stenosis secondary to fibromuscular dysplasia
  - Vascular anomalies of the central nervous system, including stenoses, moyamoya disease, and aneurysms
  - Nevus anemicus found in up to 50% of patients
  - Malignant transformation of neurofibroma 2° to second mutation, most commonly in **p53**
  - **Strong triple association** between NF1, **juvenile xanthogranulomas**, and **juvenile chronic myelogenous leukemia**
  - Of note, Watson syndrome = NF1 features + **pulmonic stenosis**
- **NF2 (Bilateral acoustic schwannomas)**
  - AD disorder caused by mutations in **SCH** gene (encodes schwannomin/**merlin**; tumor suppressor gene)
  - Symptoms appear later than NF1 (usually in second to third decade)
  - Cutaneous findings: neurofibromas (in lower #s than NF1) – more commonly **subcutaneous** type w/ **overlying pigment/hair** rather than intradermal (seen mainly in NF1), **CALM** (usually ≤2 lesions)
  - Neurological findings: **bilateral vestibular schwannomas (acoustic neuromas)** is diagnostic; may → deafness, **tinnitus**, unsteadiness, headache; patients should NOT swim alone), meningiomas, astrocytomas, and ependymomas
  - Ocular findings: juvenile posterior subcapsular lenticular opacity/cataract
  - Poor prognosis with worsening hearing, vision, ambulation; CNS tumors are most common cause of death
- Histology of hypomelanotic macules: normal # of melanocytes with ↓pigmentation
- Treatment of facial angiofibromas: pulsed dye laser, ablative laser, excision, and **topical rapamycin**
- Neurologic findings: **cortical tubers**, subependymal nodules (may → hydrocephalus), subependymal giant cell astrocytomas, seizures/**infantile spasms**, hypsarrhythmia, intellectual impairment, and **paraventricular calcification**
  - Infantile spasms, large number of cortical tubers, and early age of onset of seizures or intractable seizures associated with **worse prognosis**
  - **#1 cause of mortality** = complications related to seizures
- Renal findings: renal cysts, **angiomyolipomas**, and renal cell carcinoma
  - Systemic mTOR inhibitors (i.e., sirolimus and everolimus) used for management of renal and hepatic angiomyolipomas and subependymal giant cell astrocytomas
  - Complications of renal disease (renal failure, catastrophic hemorrhage within a renal angiomyolipoma, and renal hypertension) = **#2 cause of premature death**
- Ocular findings: **retinal phakomas** (hamartomas)
- Cardiac findings: **cardiac rhabdomyomas** → Wolf-Parkinson-White arrhythmia
- GI findings: hepatic cysts, hepatic angiomyolipomas (usually asymptomatic), and GI polyps/hamartomas
- Dental findings: **pits in enamel** and **gingival fibromas**
- Lung findings: pulmonary **lymphangioleiomyomatosis** and pulmonary cysts
  - Pulmonary complications: pneumothorax, chylothorax, hemoptysis, and pulmonary insufficiency
- Definite diagnosis of TSC requires either the presence of a pathogenic mutation in **TSC1** or **TSC2** **OR** the presence of two major criteria or one major criteria and two minor criteria (**Table 4-16**)
- A possible diagnosis of TSC requires the presence of one major or two minor criteria (**Table 4-16**)
- Cutaneous features are seen in 90% of affected patients, and may be the first presenting sign **Table 4-17**

## Tuberous sclerosis complex (TSC)

- AD disorder caused by mutations in **hamartin (TSC1)** or **tuberin (TSC2)** (tumor suppressor genes)
  - Tuberin and hamartin form a complex that inhibits signal transduction of downstream effectors of **mTOR** (mammalian target of rapamycin) → abnormal regulation of cellular differentiation, proliferation, and migration of affected cell types with the formation of multiple hamartomas
- Mosaic/segmental disease can occur
- Cutaneous findings: **adenoma sebaceum** (facial angiofibromas), hypopigmented "**ash-leaf**" macules (confetti pattern pretibially; first cutaneous finding), **Shagreen patch** (connective tissue nevus), periungual fibromas ("**Koenen tumors**"), and **CALM**
  - Histology of angiofibromas: dermal fibrosis with stellate fibroblasts, atrophic sebaceous glands, dilated capillaries, and loss of elastin
  - Histology of Shagreen patch: broad sclerotic collagen bundles and reduced elastin

**Table 4-16.** Diagnostic Criteria For TSC

Major Features	Minor Features
≥3 Angiofibromas or fibrous cephalic plaque	≥ 3 Dental enamel pits
≥3 Hypomelanotic macules >5 mm in diameter	≥ 2 Intraoral fibromas
≥2 Ungual fibromas	"Confetti"-like skin lesions
Shagreen patch	Nonrenal hamartomas
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias	Retinal achromic patch
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
≥2 Angiomyolipomas	

**Table 4-17.** Cutaneous Manifestations of TSC by Average Age of Presentation

Average Age of Onset	Cutaneous	Other
Infancy to early childhood	<b>Hypomelanotic macules</b> "Confetti"-like skin lesions	Cardiac rhabdomyomas Subependymal nodules Seizures
Prepubertal	Angiofibromas (Fig. 4-29) Shagreen patch Fibrous cephalic plaque Dental pits	Renal hamartomas
Adolescence	<b>Ungual fibromas</b> (Fig. 4-30)	
Adulthood	Intraoral fibromas	Pulmonary lymphangioleiomyomatosis (females) Renal cysts

**Figure 4-29.** Tuberous sclerosis. Facial angiofibromas ("adenoma sebaceum") are typically 1- to 4-mm, skin-colored to red, dome-shaped papules with a smooth surface. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)**Figure 4-30.** Periungual fibrous nodules (Koenen's tumors) on the toes of an adolescent with tuberous sclerosis. (Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology*, 4th ed. 2007)**Table 4-18.** Findings in Incontinentia Pigmenti

Stage	Manifestation	Timing	Comments
Vesicular	Inflammatory vesicles or pustules (Fig. 4-31)	Birth to 1 month	Reactivation may occur with illness or trauma
Verrucous	Warty papules	Up to 2 years (usually resolved by 8 weeks)	
Hyperpigmented	Blue to brown streaks	Up to adolescence (may resolve by 1 year)	May not involve previously vesicular or verrucous areas
Hypopigmented	Atrophic hypopigmented streaks	May persist through adulthood	

**Table 4-19.** Other Clinical Manifestations of Incontinentia Pigmenti

Organ	Manifestation	Frequency
Other cutaneous	<b>Cicatricial alopecia</b> Nail dystrophy <b>Subungual tumors</b> (resembles SCC!)	10%–20% 10% Up to 10%
Teeth	<b>Pegged or conical teeth</b> <b>Anodontia</b> Delayed dentition	50%
Central nervous system	<b>Seizures</b> Mental retardation Spastic paresis	30%
Eyes	Retinal vascular anomalies (e.g., vascular changes → blindness) Nonretinal anomalies (strabismus, cataracts, and optic atrophy)	30%
Breast	Supernumerary nipples Nipple hypoplasia Breast hypoplasia or aplasia	11%–30%

## Incontinentia pigmenti (IP)

- XLD loss of function mutation in nuclear factor- $\kappa$ B (NF- $\kappa$ B) essential modulator (*NEMO*; *IKBKG*)
  - Mutation in *NEMO* prevents activation of NF- $\kappa$ B, a regulator of cell proliferation, inflammation, and TNF- $\alpha$  induced apoptosis
  - Mutation is **lethal in males**; seen primarily in women and XXY (Klinefelter's) males
  - Functional mosaicism from lyonization in affected females (random inactivation of affected X chromosome) results in **Blaschkoid pattern** of cutaneous involvement
- IP is a neuroectodermal disorder that affects the skin, teeth (hypodontia/anodontia), central nervous system, and eyes
  - Cutaneous lesions are typically arranged in streaks and whorls, following Blaschkoid pattern
    - Four distinct morphologic stages (Table 4-18)
    - Patients may not develop all four cutaneous stages
    - Alopecia may affect the scalp and other parts of the body



**Table 4-20.** Neurocutaneous Syndromes: Genetic Basis and Clinical Findings

Disease	Gene/ Inheritance	Gene Function	Cutaneous Features	Neurologic Features	Other Distinct Features
Neurofibromatosis type 1	Neurofibromin/ AD	Cytoplasmic protein; negatively regulates Ras activation	Café-au-lait macules Intertriginous freckling Dermal neurofibromas Plexiform neurofibromas	Learning disabilities Attention deficit disorder Autistic spectrum Pilocytic astrocytomas Meningiomas	Lisch nodules Optic gliomas Tibial dysplasia Sphenoid wing dysplasia Scoliosis
Legius syndrome	SPRED1/AD	Interacts with Ras	Café-au-lait macules Intertriginous freckling	Learning disabilities	
Neurofibromatosis type 2	Merlin/AD	Cytoskeletal protein; tumor suppressor	Schwannomas Neurofibromas Café-au lait macules (33%)	Vestibular and cranial schwannomas Cranial meningiomas Spinal cord tumors	Juvenile posterior subcapsular cataract Hearing loss
Tuberous sclerosis	Hamartin or tuberlin/AD	Inhibits signal transduction of downstream effectors of mTOR	Hypomelanotic macules Angiofibromas Fibrous cephalic plaque Shagreen patch Ungual fibromas Intraoral fibromas	Subependymal nodules Seizures Subependymal giant cell astrocytoma	Cardiac rhabdomyoma Renal angioliopomas and cysts Pulmonary lymphangioleiomyomatosis (females)
Incontinentia pigmenti	NEMO/XLD	Activates NF $\kappa$ B, a regulator of cell proliferation, inflammation, and apoptosis	Four stages: vesicular, verrucous, hyperpigmented, and hypopigmented Alopecia Nail dystrophy Subungual tumors	Seizures Mental retardation Spastic paresis	Dental anomalies Ocular (retinal) defects Breast anomalies Male children with hypohidrotic ectodermal dysplasia with immunodeficiency



**Figure 4-31.** Incontinentia pigmenti. The lesions of incontinentia pigmenti tend to follow a curvilinear pattern along lines of Blaschko, lines of the embryological development of ectoderm, as a manifestation of functional mosaicism (i.e., the X chromosome with the mutation in the NEMO gene is the activated X chromosome in the skin at these sites). The lesions of the vesicular phase may range from largely papular with a minor vesicular component to vesiculopustular as shown here and occasionally to bullous. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)

- Histology varies by stage:
  - Vesicular stage: **eosinophilic spongiosis**; intraepidermal vesicles containing eosinophils; **apoptotic keratinocytes** in epidermis
  - Verrucous stage: papillomatosis, hyperkeratosis, and acanthosis of the epidermis; apoptotic cells in epidermis forming squamous eddies

- Hyperpigmented stage: marked pigment incontinence with numerous melanophages in the dermis; apoptotic cells may be seen in epidermis
- Hypopigmented stage: epidermal atrophy, loss of melanin in basal layer, complete absence of pilosebaceous units and eccrine glands; apoptotic cells may be seen in epidermis
- Severely affected patients may develop **seizures, developmental delay and intellectual impairment, and ↓visual acuity/blindness** (due to retinal vascular changes and optic atrophy)
- Females with missense mutations in NEMO (milder phenotype of IP) can bear children (usually male) with hypohidrotic ectodermal dysplasia with immunodeficiency

## 4.12 PREMATURE AGING SYNDROMES AND DNA REPAIR DISORDERS

### Hutchinson-Gilford progeria

- AD disorder caused by specific mutation (1824C>T) in the **LMNA gene** (encodes **lamin A**)
  - Mutation introduces a splice site that results in the protein being abnormally farnesylated
  - Lamin A protein **contributes to the structure/function of the nuclear envelope**
  - With abnormal farnesylation, lamin A cannot insert normally into the nuclear envelope
- Cutaneous manifestations begin around 6–18 months:
  - Localized sclerodermatous changes of lower trunk/thigh



- Cyanosis around mouth or nasolabial folds
- Dyspigmentation
- Also see failure to thrive early on
- Over time, patients show **signs of premature aging**
  - Early skin wrinkling and xerosis
  - Hair loss (scalp, eyebrows, and eyelashes)
  - Skin atrophy with prominent veins
  - **Atherosclerosis and angina**
  - Bone density loss/osteoporosis (w/ susceptibility to fractures), coxa valga, and osteolysis of distal phalanges
- Other dermatologic manifestations: lipodystrophy, onychodystrophy, and breast hypoplasia
- Facial features: **enlarged head**, micrognathia with dental crowding, small ears, and beaked nose (Fig. 4-32)
- A **high-pitched voice** is characteristic
- **Rapid and progressive features of premature aging develop** – complications include cerebrovascular and cardiovascular events (CHF and MI), limited mobility and exercise tolerance, and poor growth
- **Complications of cardiovascular disease are the most common cause of mortality** (mean age of death = 13 years)

### Werner syndrome

- AR disorder as a result of mutations in the *RECQL2/WRN* gene (encodes a **DNA helicase** that helps maintain genomic stability)
  - Mutations in *RECQL2/WRN* → ↑expression of inhibitors of DNA synthesis and ↑telomere-driven replicative senescence → **accelerated aging**
  - Symptoms/signs seen in third to fourth decade
- Cutaneous findings: premature canities, progressive alopecia, bird-like facial appearance, **sclerodermatous/**



**Figure 4-32.** Progeria syndrome. (From Arnold De Loof, Wouter De Haes, Tom Janssen, Liliane Schoofs. General and Comparative Endocrinology, Volume 199, Pages 70-85. Elsevier. 2014)

- **atrophic change acral/facially**, mottled pigmentation, telangiectasias, hyperkeratotic ulcers over pressure points, leg ulcers, calcinosis cutis, and loss of subcutaneous fat
- Extracutaneous findings: short stature, muscle wasting, atherosclerosis (can → CVA/MI), diabetes mellitus, hypogonadism, osteoporosis, arthritis, posterior subcapsular cataracts, DM2, and hypogonadism
- ↑risk of malignancy: carcinoma of breast or ovary, thyroid adenocarcinoma, **fibrosarcoma**, **osteogenic sarcoma**, meningioma, skin cancers, and hepatoma
- **Malignancy and cerebrovascular/cardiovascular events** are main causes of mortality (mid-50s typically)

### Xeroderma pigmentosum (XP)

- AR disorder due to mutations in *XPA* to *XPG* genes (as well as variant *XPV* gene) – each gene encodes a protein important in the **nucleotide excision repair pathway**: *XPA* encodes DNA damage binding protein 1 (DDB1), *XPB* encodes excision-repair cross-complementing 3 (ERCC3), *XPC* encodes endonuclease, *XPD* encodes ERCC2, *XPE* encodes DDB2, *XPF* encodes ERCC4, *XPG* encodes endonuclease, and *XPV* is unique in that it encodes a DNA polymerase
  - Subtypes (complementation groups) of XP (*XPA* to *XPG*) correspond to the affected genes
  - In the variant subtype *XPV*, the **post-replication repair pathway** is abnormal because of mutations in the gene that encodes **DNA polymerase-η**
  - Affected individuals have ↑**sensitivity to UV-induced skin damage** caused by **abnormalities in DNA repair pathways** (i.e., recognition of damaged DNA, unwinding of DNA [helicases], and incision/removal of damaged DNA [endonucleases])
  - Most common subtypes in the United States are *XPA* and *XPC*; *XPA* is most common subtype in Japan
  - Different mutations in the XP genes may lead to different phenotypes and overlap syndromes:
    - *XPB*, *XPD* and *XPG*: a/w XP-Cockayne overlap syndrome; possess signs of both XP (skin cancers, lentigines) and **Cockayne syndrome** (retinal degeneration, basal ganglia calcification)
    - *XPB*, *XPD*: also a/w **trichothiodystrophy**
- Typical cutaneous manifestations appear after 6 months, with development of persistent erythema, scaling, and ephelides on sun-exposed areas
- Eventually poikiloderma develops, followed by development of numerous cutaneous malignancies (Fig. 4-33)
  - **1000-fold increased risk of cutaneous malignancy** in patients <20 years of age, including BCC, SCC, melanoma, and fibrosarcoma; mean onset of cutaneous malignancy = 8 years of age
  - ↑risk of solid and CNS tumors, though rare
- Ophthalmologic complications: photophobia, conjunctivitis, ectropion, and symblepharon
- Neurodevelopmental complications, including developmental delay, intellectual impairment, sensorineural hearing loss, hyporeflexia, and/or ataxia



**Figure 4-33.** Xeroderma pigmentosum. An 8-year-old girl presenting with dry and parchment-like skin with hyperpigmentation and multiple pigmented basal cell carcinomas on the face. Both eyes show corneal opacification. (Photograph courtesy of Dr Wisuthsarewong, Bangkok, Thailand. From Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children in JAAD, Volume 67, issue 6 1113.e1–1113.e15. Elsevier. 2012.)

occurs in 20%–30% of XP patients (esp. XPA and XPD groups) XPV patients have no neurologic complications

- De Sanctis-Cacchione syndrome: rare XP phenotype with severe neurologic deficits (severe mental, retardation, deafness, ataxia and paralysis)
- Severely affected individuals usually die as a result of complications from metastatic melanoma or invasive squamous cell carcinoma by ~20 years of age

### Bloom syndrome (congenital telangiectatic erythema)

- AR disorder due to mutations in *BLM/RECQL3* (DNA helicase) → ↑rates of sister chromatid exchange and chromosomal instability
- Presents early in life w/ prenatal and postnatal growth impairment (short stature; do not exceed 5 feet in height)
- Cutaneous manifestations: photosensitivity, telangiectatic erythema in a malar distribution, cheilitis, CALM, and hypopigmentation
- Facies: narrow face w/ prominent ears, malar hypoplasia, and prominent/bird-like nose
- Other features: primary hypogonadism (men are sterile, women have decreased fertility), high-pitched voice, ↓IgA and IgM → bronchiectasis/chronic lung disease/recurrent respiratory and GI infections, ↑risk lymphoma and leukemia (150–300-fold ↑risk), ↑risk of some solid tissue tumors (squamous cell carcinomas and adenocarcinomas [esp. GI])
- A characteristic pattern of chromosomal breakage and rearrangement may be seen on chromosomal

instability testing, which can be performed at specialized centers

- Cutaneous and immunologic findings improve with age, but ↑risk of mortality from malignancy (#1 cause of death, esp. leukemia) in the second to third decades; patients do not survive beyond 50yo

### Rothmund-Thomson syndrome (Poikiloderma congenitale)

- AR disorder caused by mutations in *RECQL4* (DNA helicase that facilitates DNA replication and repair of UV damage)
- Cutaneous manifestations (present in first year of life): erythema, edema, and blisters that begin on the cheeks and subsequently progress to involve the extensor surfaces of the extremities and buttocks; poikiloderma (hypo- and hyperpigmentation + atrophy) is subsequently noted at these sites; acral verrucous keratoses (may → SCC), photosensitivity (in 30%), alopecia of scalp/lashes/brows, and dystrophic nails
- Short stature and skeletal dysplasia (e.g., absence or hypoplasia of thumbs, radius, and ulna); triangular-appearing face with frontal bossing/saddle nose/micrognathia; juvenile cataracts; dental anomalies; hypogonadism
- Malignancy may lead to premature death
  - Osteosarcoma (mean onset = 14 years of age) in ~30% patients
  - Non-melanoma skin cancer (esp. SCC) – mean age = 34 years of age

### Cockayne syndrome (CS)

- AR disorder due to defective transcription-coupled NER (nucleotide excision repair) = inability to resume RNA synthesis after UVR exposure (differs from XP, which has defective global genomic NER)
- Identical phenotype may occur due to mutations occur in either of 2 genes:
  - CS-A (20%): mutations in excision repair, cross complementing group 8 (*ERCC8*)
  - CS-B (80%): mutations in *ERCC6*
- Classic CS (CS I) presents at end of first decade
- CS II (severe CS) presents at birth; progresses more rapidly
- Cutaneous manifestations: photosensitivity, with telangiectatic erythema; unlike XP, has NO ↑risk of skin cancer and LACKS pigmentary changes
- Typical facies: pinched, narrow “bird-like” face w/ beaked nose, large protuberant ears, and sunken eyes; growth failure and cachexia
- Neurologic manifestations: basal ganglia calcification, progressive deterioration/demyelination of CNS/PNS with ataxia and spasticity, intellectual impairment, microcephaly, and progressive sensorineural hearing loss
- Skeletal manifestations: short stature + cachectic/thin body (“cachectic dwarfism”), joint contractures, and kyphosis
- Ophthalmologic manifestations: salt and pepper retinopathy, optic atrophy, cataracts, and nystagmus
- Hypogonadism may be seen in affected males
- Most patients die by fourth decade from progressive neurologic disease complications

## Trichothiodystrophy (Tay syndrome and PIBIDS syndrome)

- AR
  - A heterogeneous group of diseases w/ brittle hair and nails (↓content of **cysteine-rich proteins**), ichthyosis, and neurodevelopmental disability; **classified as photosensitive or non-photosensitive**
    - **TTD with photosensitivity (TTD-P)**: caused by mutations in three genes (*ERCC2*, *ERCC3*, and *GTF2H5*) encoding proteins (XPD, XPB, and TTDA), respectively, that function in the transcription repair protein IIH complex, which is involved in DNA transcription and excision repair.
    - **TTD, non-photosensitive (TTD-NP)**: results in about 10%–20% of cases from mutations in the *C7orf11* gene, M-phase specific PLK1 interacting protein (MPLKIP), which is thought to regulate transcription efficiency; **lacks ichthyosis**
- Photosensitivity (unlike XP, has **NO increased skin cancer risk**)
- Ichthyosis
- Brittle hair (short/sparse on scalp/brows/lashes w/ alternating light and dark bands on **polarizing light microscopy** (“tiger-tail” abnormality)
  - **Trichoschisis** and **trichorrhexis nodosa** may be seen
- Intellectual impairment and ataxia
- Decreased fertility/hypogonadism
- Short stature
- Other findings: hypoplastic/dysplastic nails, palmoplantar keratoderma, keratosis pilaris, atopic dermatitis, cataracts, osteosclerosis, joint contractures, aged facial appearance, and **hypogammaglobulinemia** with recurrent infections

## 4.13 PRIMARY IMMUNODEFICIENCY DISORDERS (PIDs) WITH CUTANEOUS MANIFESTATIONS

- Categorized by defects in the various components of the innate and adaptive immune system; overlap or combined defects often occur
  - **Tables 4-21 through 4-23** summarize PIDs that are most commonly associated with cutaneous findings
  - Majority have AR inheritance, but some are X-linked (anhidrotic ectodermal dysplasia with immunodeficiency, chronic granulomatous disease, severe combined immunodeficiency syndrome (SCID) (IL2Rγ), Wiskott-Aldrich, Bruton’s agammaglobulinemia, and IPEX syndrome)
- Signs that raise suspicion for PID
  - ↑frequency/severity/duration of bacterial, viral, and/or fungal infections
  - Opportunistic infections including atypical mycobacterial or deep fungal infections
  - Failure to thrive

- Cutaneous infections may include any or all of the following:
  - Recurrent Staphylococcal or other bacterial pyodermas
  - Extensive viral infections (warts, molluscum, and HSV)
  - Widespread dermatophyte infections
  - Mucocutaneous candidiasis
- Hematopoietic stem cell transplantation is indicated in those with severe PIDs including:
  - Severe combined immunodeficiencies
  - Chronic granulomatous disease
  - Wiskott-Aldrich syndrome
  - IPEX
  - Hemophagocytic lymphohistiocytosis (Chediak-Higashi and Griscelli)
  - MonoMAC syndrome
- **Transplacental transfer of maternal T-lymphocytes** may occur in neonates with severe combined immunodeficiency (**SCID**), and may → clinical signs of graft-versus-host disease (e.g., morbilliform, LP-like, seborrheic dermatitis-like, and sclerodermatous change)
- Cutaneous infections predominantly caused by one family of organisms may ↑ suspicion of specific PIDs (**Table 4-21**)
- Distinct non-infectious cutaneous findings may lead to the diagnosis of a specific PID (**Table 4-22**)

**Table 4-21.** Cutaneous Infections associated with Primary Immunodeficiency Disorders

<b>Mucocutaneous Candidiasis</b>	Chronic mucocutaneous candidiasis syndromes
	AD hyper-IgE syndrome (STAT3)
	Chronic granulomatous disease
	Leukocyte adhesion deficiency
	Chediak-Higashi
<b>Recurrent Bacterial Pyodermas</b>	Griscelli
	AR hyper-IgE syndrome (DOCK8)
	WHIM
	EDV
	Monomac
<b>Extensive Viral Infection (HPV, Molluscum)</b>	

**Table 4-22.** Cutaneous Findings associated with Primary Immunodeficiency Disorders

<b>Erythroderma</b>	Omenn syndrome > other SCID*
	Hyper IgE syndrome (STAT3 > DOCK8)
	Wiskott-Aldrich syndrome
	IgA deficiency
	Omenn syndrome
<b>Atopic Phenotype (Eczematous Dermatitis and Elevated Eosinophils and IgE)</b>	IPEX syndrome
	Ataxia telangiectasia
	SCID (RAG1)
	Common variable immunodeficiency
	Chronic granulomatous disease
<b>Noninfectious Cutaneous Granulomas</b>	Griscelli syndrome
	Chediak-Higashi syndrome
<b>Pigmentary Dilution (Silvery Hair and Hypopigmentation)</b>	

\*Maternal graft-versus-host disease should be considered.

## 4.13 Primary Immunodeficiency Disorders (PIDs) With Cutaneous Manifestations

**Table 4-23.** Primary Immunodeficiencies Most Commonly Associated With Cutaneous Findings

Class	Mutation	Characteristic Infections	Distinct Cutaneous Features	Extracutaneous Features
<b>Combined immunodeficiencies</b>				
Omenn syndrome	<b>RAG1</b> <b>RAG2</b>	Any	<b>Erythroderma</b> Alopecia	Hepatosplenomegaly and lymphadenopathy
SCID	<b>IL2RG</b> (IL-2R $\gamma$ chain) – most common; <b>XLR</b> inheritance <b>ADA</b> → ↑adenosine → lymphocyte toxicity; <b>AR</b> inheritance <b>ZAP70</b> <b>JAK3</b> ; <b>AR</b> inheritance	<b>Any</b> <i>C. albicans</i> (esp. oral), <i>S. aureus</i> , and <i>S. pyogenes</i> Cutaneous infections caused by various organisms, including those listed above Sepsis of blood Viral diarrhea Otitis media Pneumonia (PCP and parainfluenza, in addition to bacteria)	Erythroderma (less common) See above re: GVHD-like presentation	<b>No palpable lymph nodes</b> No tonsillar buds/lymphoid tissue <b>Failure to thrive</b>
<b>Combined immunodeficiencies with associated or syndromic features</b>				
Wiskott-Aldrich	<b>WAS</b> (XLR)	<b>Recurrent encapsulated bacterial infections</b> (e.g., otitis media, pneumonia, and meningitis), HSV (as eczema herpeticum), HPV, and PCP Infection can → death in first decade	<b>Eczematous dermatitis</b> (scalp, face, and flexures) w/ 2° infections	Thrombocytopenia (→ <b>petechiae/purpura/epistaxis</b> ), small platelets, and bloody diarrhea ↑ <b>food allergies/asthma/urticaria</b> ↑ <b>IgA, IgD, and IgE</b> ; ↓ <b>IgM</b> Both cell-mediated and humoral immune response are compromised ↑ <b>risk non-hodgkin's lymphomas</b> (and other hematologic malignancies)
Ataxia telangiectasia	<b>ATM</b>		Telangiectasias of skin and conjunctivae Noninfectious granulomas	Truncal > peripheral ataxia Neurologic deterioration <b>Sensitivity to ionizing radiation</b> ↑ risk of <b>hematologic malignancies</b> <b>Female heterozygotes at increased risk for breast cancer</b>
AD hyper IgE	<b>STAT3</b>	Pyodermas, cellulitis, furuncles, abscesses, and paronychia <i>S. aureus</i> , <i>Candida</i> , and <i>Streptococcus</i> <b>30% of abscesses are cold</b> Bronchitis, otitis media, empyemas, sinusitis, pneumatoceles, lung abscesses, and pneumonia (can → early death) <i>S. aureus</i> , <i>H. influenzae</i> , and fungal infections	<b>Coarse facial features</b> (broad nasal bridge and big nose) Diffuse dermatitis	<b>Retained 1° teeth w/ issues in 2° teeth</b> Osteopenia → fractures, scoliosis, and hyperextensibility ↑IgE and eosinophilia
AR hyper IgE	<b>DOCK8</b>	Any	No dysmorphic features	

Continued



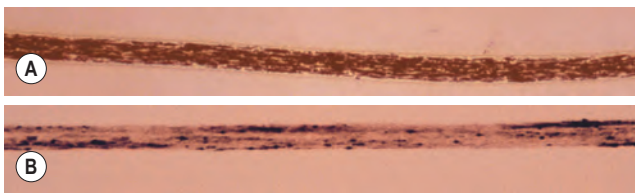
**Table 4-23.** Primary Immunodeficiencies Most Commonly Associated With Cutaneous Findings—cont'd

Class	Mutation	Characteristic Infections	Distinct Cutaneous Features	Extracutaneous Features
<b>Antibody deficiencies</b>				
IgA deficiency	<i>IGAD1</i>	<b>Sinopulmonary bacterial infections</b> and <i>Giardia</i> gastroenteritis	Eczematous dermatitis Autoimmune conditions	Must test for IgA deficiency (is the <b>most common immunoglobulin deficiency</b> ) before giving ANY patient IVIG!
CVID (heterogeneous disorder currently classified into types CVID1-CVID11)	<i>ICOS</i> <i>CD19</i> <i>CD20</i> <i>CD21</i> <i>CD81</i> <i>LRBA1</i> <i>TACI</i> <i>BAFFR</i> <i>NFKB2</i> <i>IL21</i> <i>PRKCD</i>	Bacterial infections	Noninfectious granulomas Autoimmune conditions	Hypogammaglobulinemia ↑ risk for hematologic malignancies
Bruton's hypogammaglobulinemia	<i>BTK</i>	<i>Helicobacter bilis</i> associated pyoderma gangrenosum	Noninfectious granulomas	↑ risk for hematologic malignancies
<b>Defects in phagocyte number or function</b>				
Chronic granulomatous disease	<b>CYBB</b> (p91 - phagocyte oxidase (phox) beta subunit) <b>CYBA</b> (p22-phox alpha subunit) <i>NCF1</i> (neutrophil cytosolic factor 1/p47-phox) <i>NCF2</i> (p67-phox) <i>NCF4</i> (p40-phox)	Pneumonia ( <i>Nocardia</i> , <i>Aspergillosis</i> , and <i>Staphylococcus</i> ), perianal abscesses, perioral dermatitis, and pyodermas due to <b>catalase-(+) organisms (<i>Staphylococcus aureus</i> #1)</b>	Noninfectious granulomas (cutaneous AND extracutaneous, esp. GI tract) Gingivitis/stomatitis	Hepatosplenomegaly, diarrhea, and lymphadenopathy (cervical #1; suppurative → abscess/fistula), granulomas of lung/liver/GU/GI <b>Female carriers of x-linked CGD may have higher risk of lupus</b> Can test diagnosis with <b>nitroblue tetrazolium test</b>
Leukocyte adhesion deficiency type 1	<i>ITGB2</i>	Pyodermas Bacterial ulcerations can mimic pyoderma gangrenosum	<b>Delayed separation of umbilical cord</b> <b>Poor wound healing</b>	Periodontitis → loss of teeth
Chediak-Higashi	<i>LYST</i>	Pyodermas Bacterial ulcerations can mimic pyoderma gangrenosum	<b>Pigmentary dilution</b> (silvery hair and hypopigmentation of skin) Hyperpigmentation may develop in acral sun-exposed areas	<b>Accelerated lymphohistiocytic phase</b> Neurologic deterioration <b>Giant granules or melanosomes in leukocytes and melanocytes</b>
Grisoelli (Fig. 4-34)	<i>Rab27A</i>	Pyodermas	<b>Pigmentary dilution</b> (silvery hair and hypopigmentation of skin)	<b>Accelerated lymphohistiocytic phase</b> Neurologic deterioration (primarily with MYO5A mutation)
<b>Innate immunity</b>				
Hypohidrotic ectodermal dysplasia with immunodeficiency	<b>NEMO</b>		Conical incisors Decrease or absence of sweat glands and hair follicles	<b>Allelic to incontinentia pigmenti</b>
Chronic mucocutaneous candidiasis/familial candidiasis	<i>CARD9</i> <i>IL-17RA</i> <i>IL-17F</i> <i>CLEC7A</i> <i>STAT1</i> <i>TRAF3IP2</i>	Mucocutaneous candidiasis and deep dermatophytosis		
WHIM	<i>CXCR4</i>	<b>HPV (extensive verrucae)</b>		<b>Myelokathexis</b> (peripheral neutropenia with retention of neutrophils in bone marrow)

**Table 4-23.** Primary Immunodeficiencies Most Commonly Associated With Cutaneous Findings—cont'd

Class	Mutation	Characteristic Infections	Distinct Cutaneous Features	Extracutaneous Features
EDV	<i>EVER1</i> <i>EVER2</i>	HPV 5, 8, 10, 14, 20, 21, 25 and 47 (extensive verruca plana, along with thicker verrucous warts)		Malignant transformation of warts to <b>SCC</b>
Monomac	<i>GATA2</i>	HPV, atypical mycobacteria, and deep fungal infections		Pulmonary alveolar proteinosis ↑ risk for hematologic malignancies
<b>Immune dysregulation</b>				
Immunodeficiency, polyendocrinopathy, and X-linked (IPEX)	<i>FOXP3</i>		Eczematous dermatitis	Severe diarrhea (enteropathy) Type 1 diabetes mellitus Hypothyroidism Autoimmune hemolytic anemia

*SCID*, severe combined immunodeficiency; *CVID*, common variable immunodeficiency; *WHIM*, warts, hypogammaglobulinemia, infections, myelokathexis; *EDV*, epidermodysplasia verruciformis; *IPEX*, immunodysregulation, polyendocrinopathy, enteropathy, X-linked



**Figure 4-34.** Silvery hair syndromes. The giant melanosomes are easily seen in the hair shaft of individuals with Chediak-Higashi syndrome (**A**) and Griscelli syndrome (**B**). Note the more regular spacing of the melanosomes in the hair from a patient with Chediak-Higashi syndrome. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)

## 4.14 DISORDERS OF CORNIFICATION

- Inherited ichthyoses generally present at birth or in infancy/early childhood
  - Heterogeneous group of genetic disorders linked by a common finding of abnormal epidermal differentiation or metabolism → hyperkeratosis and/or epidermal hyperplasia
  - Dysfunction of cornified cell envelope disrupts skin barrier function → ↑ transepidermal water loss
  - Inherited ichthyoses characterized by localized or generalized hyperkeratosis, scaling, or both, along with variable additional cutaneous and/or systemic manifestations; +/- erythema
  - Collodion membrane at birth seen with some forms of congenital ichthyosis (lamellar ichthyosis and **non-bullous congenital erythroderma most commonly**; also Sjögren-Larsson syndrome, Gaucher disease type 2, Hay-Well syndrome, trichothiodystrophy, Netherton syndrome, ectodermal dysplasia, and neutral lipid storage disease); phenotype reveals itself once the collodion resolves, after several weeks (**Fig. 4-35**)
  - Routine histology is generally non-diagnostic, but may demonstrate epidermal hyperplasia and variable orthohyperkeratosis; **ichthyosis vulgaris shows a diminished or absent granular layer** and epidermolytic ichthyosis shows epidermolytic hyperkeratosis
  - Treatments for inherited ichthyosis: **emollients and keratolytics**; topical and systemic **retinoids** can help reduce hyperkeratosis and are useful for some disorders; neonatal care includes humidified incubators, emollients and close observation for infection, dehydration, and electrolyte abnormalities
- Palmoplantar keratoderms (PPK) are a heterogeneous group of inherited and acquired disorders marked by hyperkeratosis of the palms and soles
  - Three types of PPK: focal (localized areas of hyperkeratosis, usually over pressure points), diffuse (hyperkeratosis involves entire palmoplantar surface), and punctate (1- to 2-mm keratotic papules)
  - PPK can be an isolated finding or associated with other abnormalities
  - Treatment: topical keratolytics (salicylic acid 2%–5%, lactic acid 5%–12%, and urea 10%–40%), topical retinoids, and topical corticosteroids when inflammation is present; use of oral retinoids may be helpful in some disorders; CO<sub>2</sub> laser ablation and surgical paring or excision helpful for more severe PPK
- See [Table 4-24](#), and [Table 4-25](#)



**Figure 4-35.** Collodion baby: collodion membrane in a 1-day-old newborn. (From Renata Prado MD, Lixia Z. Ellis MD, PhD, Ryan Gamble MD, Tracy Funk MD, Harvey Alan Arbuckle MD and Anna L. Bruckner MD. *Journal of the American Academy of Dermatology*, Volume 67, Issue 6, Pages 1362-1374. Elsevier. 2012.)

Text continued on p. 273

**Table 4-24.** Features of Selected Ichthyoses and Erythrokeratodermas

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Ichthyosis vulgaris	FLG	Autosomal semidominant	Infancy/childhood	Fine, adherent scales on <b>extremities</b> and trunk with sparing of flexures; larger scale on lower legs; <b>hyperlinear palms/soles</b> , and furrowed heels	<b>Keratosis pilaris</b> ; <b>atopic diathesis</b>	Diminished/ <b>absent stratum granulosum</b> w/overlying <b>orthohyperkeratosis</b> ; absent/reduced filaggrin immunostaining	Genetic testing
Steroid sulfatase deficiency (X-linked recessive ichthyosis)	STS	XLR Contiguous gene deletion may → Kallmann syndrome	Infancy	Fine to large, <b>dark/brown, adherent scales</b> on extremities, trunk, neck, and lateral face <b>sparing flexures</b> , palms, soles, and face	<b>Corneal (comma-shaped) opacities</b> ; <b>cryptorchidism</b> ; ↑risk of <b>testicular cancer</b> , and hypogonadism <b>Female carriers</b> : corneal opacities; <b>prolonged labor</b> with affected child (placental sulfatase deficiency)	Retained corneodesmosomes within stratum corneum	Lipoprotein electrophoresis (increased mobility of β-fraction); plasma cholesterol sulfate increased; decreased steroid sulfatase activity in leukocytes; FISH, array CGH, genetic testing Maternal carriers may have abnormal triple/quadruple screen during affected pregnancy with decreased serum estradiol
Lamellar ichthyosis (Fig. 4-36)	<b>TGM1</b> <b>ABCA12</b> <sup>*</sup> <b>CYP4F22</b> <sup>*</sup> <b>CERS3</b>	AR	Birth	Frequently collodion membrane at birth with ectropion and eclabium; after collodion resolves, presence of large, <b>thick, plate-like brown scales</b> in generalized distribution w/ <b>significant flexural involvement</b> ; absent or mild erythroderma; variable palm/sole involvement (PPK)	<b>Heat intolerance</b> (hypematremic dehydration); frequent <b>scarring alopecia</b> ; dystrophic nails Hypohidrosis	TGM1: thin cornified envelope and disorganized lamellar bilayers ABCA12: absence of lamellar body content NIPAL4: defective lamellar bodies and perinuclear membranes within stratum granulosum	<i>In situ</i> transglutaminase-1 expression and activity assay; genetic testing
Congenital ichthyosiform erythroderma (CIE)	<b>TGM1</b> <b>ALOXE3</b> <sup>*</sup> <b>ALOX12B</b> <sup>*</sup> <i>NIPAL4</i> <i>(ICHTHYIN)</i> <sup>†</sup> <i>PNPLA1</i> <sup>†</sup>	AR	Birth	Frequently <b>collodion membrane</b> (#1 cause) at birth; after collodion resolves, fine, <b>white scale</b> in generalized distribution ( <b>flexures involved</b> ); erythroderma; variable palm/sole involvement	Heat intolerance/hypohidrosis; variable scarring alopecia and ectropion	Same as for lamellar ichthyosis	Genetic testing
Congenital self-healing collodion baby	<b>TGM1</b> <b>ALOXE3</b> <b>ALOX12B</b>	AR	Birth	<b>Collodion membrane</b> at birth; after resolution, skin appears normal without features of ichthyosis	None	Nondiagnostic	Genetic testing

Harlequin ichthyosis	ABCA12	AR	Birth	Very thick, yellow-brown plates of scale with large, deep and bright red fissures that tightly encase the neonate; <b>extreme ectropion, eclabium, and ear deformities</b> ; survivors develop severe CIE-like phenotype; <b>early initiation of systemic retinoids</b> and specialized neonatal intensive care reduce mortality	Premature delivery; risk of neonatal hypothermia, and hypematremic dehydration; <b>often neonatal death from sepsis or respiratory insufficiency</b>	Vesicular lamellar body ghosts, paucity of secreted lamellar structures in stratum corneum	Genetic testing
Epidermolytic ichthyosis (bullous CIE)	<i>KRT1</i> <i>KRT10</i>	AD	Birth	<i>At birth:</i> erythroderma, <b>blistering</b> , and erosions <i>Later:</i> <b>hyperkeratosis</b> with cobblestone pattern (most prominent over joints), ridging of the flexures; generalized or localized; variable degree of erythroderma, palmoplantar involvement, and blistering/bullae; <b>retinoids can exacerbate</b> skin fragility	Frequent skin infections; <b>malodor</b> ; gait and posture abnormalities	Hyperkeratosis, keratinocyte vacuolization, and a prominent granular layer with <b>clumped keratin in suprabasal cells</b> ; lamellar body accumulation	Genetic testing
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)	<i>KRT2</i>	AD	Birth	Erythroderma and <b>superficial blistering</b> at birth; later, hyperkeratosis with accentuation over joints, flexures, and dorsal hands/feet; <b>"molting"</b> of the skin; palms and soles spared		Cytolysis of granular cells	Genetic testing
Ichthyosis hystrix Curth-Macklin	<i>KRT1</i>	AD	Birth	Mild to severe, mutilating palmoplantar keratoderma; hyperkeratosis with verrucous, cobblestone, or hystrix-like pattern on extremities and trunk	Pseudoainhum; digital contractures	Binuclear cells; particular concentric perinuclear "shells" of aberrant putatively keratin material	Genetic testing
Ichthyosis en confetti	<i>KRT10</i>	AD		At birth, erythroderma and scaling; later, confetti-like areas of scaling (result from revertant mosaicism); palmoplantar keratoderma	Joint contractures	Affected skin: loss of epidermal differentiation above the basal layer with nucleolar vacuolization, loss of granular layer, and acanthosis, Revertant skin: normal	

Continued



Table 4-24. Features of Selected Ichthyoses and Erythrokeratodermas—cont'd

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Netherton syndrome (Fig. 4-37)	<i>SPINK5</i> (encodes LEKT1, serine protease inhibitor)	AR	Birth/infancy	<b>Congenital erythroderma</b> and scaling; two principal phenotypes: <b>ichthyosis linearis circumflexa</b> (annular or serpiginous plaques w/ <b>double-edged scale</b> ) and O/E-like; pruritus and eczematous plaques are common <b>Don't use tacrolimus ointment</b> (↑absorption → toxic) or keratolytics (irritating)	<b>Trichorrhexis invaginata</b> , trichorrhexis nodosa, and pili torti (short/sparse hair and brows; <b>FigE</b> : neonatal temperature instability, electrolyte imbalance (hyponatremia), and failure to thrive; recurrent infections; <b>food and other allergies/ anaphylaxis</b> ; nonspecific aminoaciduria	Psoriasiform histopathology; light microscopy of hair shafts may reveal trichorrhexis invaginata (" <b>bamboo hair</b> ")	Genetic testing
Stölgren-Larsson syndrome	<i>ALDH3A2/ FALDH</i>	AR	Birth	At birth, erythema and hyperkeratosis; later, fine to plate-like/dark scaling or nonscaling hyperkeratosis; favors abdomen, neck, flexures; lichenification; palmoplantar keratoderma; pruritus can be severe	<b>Progressive spastic di- and tetraplegia</b> ; developmental delay; intellectual disability; seizures; <b>perforated glistening white dots</b> ; white matter disease of the brain; <b>photophobia</b>	Nonspecific; hyperkeratosis, acanthosis, and preservation of granular layer	Fatty aldehyde hydroxylase activity assay in cultured fibroblasts; genetic testing (preferred method)
Neutral lipid storage disease with ichthyosis/ Chanarin-Dorfman syndrome	<i>ABHD5 (OGI-58)</i>	AR	Birth	Generalized, fine, white scales with variable erythema	<b>Developmental delay</b> ; <b>hepatomegaly</b> with liver fibrosis; elevated liver enzymes, and creatine kinase; myopathy; hearing impairment; cataracts	<b>Globular electron-lucent inclusions in epidermis</b>	<b>Peripheral blood smear to detect lipid vacuoles in granulocytes, eosinophils, and monocytes</b> ; oil stains of frozen tissue; genetic testing
Refsum disease	<i>PHYH PEX7</i>	AR	childhood to adulthood	Fine, white scales on extremities and trunk, resembling ichthyosis vulgaris (50%)	Peripheral motor and sensory neuropathy; cranial nerve dysfunction (deafness, anosmia); <b>cerebellar ataxia</b> ; atypical retinitis pigmentosa (" <b>salt and pepper</b> pigment"); cardiomyopathy, arrhythmias w/ heart block; muscle wasting	Orthokeratotic hyperkeratosis and lipid-containing vacuoles in basal keratinocytes	<b>Increased plasma phytanic acid</b> : phytanoyl-CoA hydroxylase activity assay in cultured fibroblasts; genetic testing <b>Diet is essential: ↓green vegetables, dairy products, and ruminant fats</b>

Keratitis-ichthyosis-deafness (KID) syndrome	GJB2 (encodes connexin 26)	AD (nearly all reported cases are sporadic)	Birth/infancy	Transient neonatal erythroderma; erythematous, hyperkeratotic plaques w/ well-demarcated, borders on face and extremities; follicular keratoses; thickening of the skin with an appearance of "coarse-grained leather;" stippled palmoplantar keratoderma	Congenital <b>sensorineural hearing impairment</b> ; progressive keratitis with corneal neovascularization that may lead to <b>blindness</b> ; conjunctivitis; recurrent mucocutaneous infections, especially with <i>Candida albicans</i> ; increased susceptibility to oral and cutaneous <b>squamous cell carcinoma</b> ; nail, hair, and dental anomalies; cheilitis	Nonspecific; acanthosis, papillomatosis, and follicular plugging
Erythrokeratoderma variabilis	GJB3 GJB4 (encode connexin 31 GJA1 and 30.3)	AD	Birth/infancy	<b>Transient, variable, erythematous patches</b> ; more <b>stable, geographic, hyperkeratotic plaques</b> over knees, elbows, Achilles tendons, extremities, buttocks, and lateral trunk; face and scalp often spared; less common generalized hyperkeratosis; palmoplantar keratoderma in ~50% of patients	Burning or stinging sensation preceding or accompanying erythema	Nonspecific; may reveal reduced lamellar bodies in stratum granulosum and reduced keratinization
Progressive symmetric erythrokeratoderma	(LOR) (GJB4) other unknown gene(s)	AD or AR	Infancy/childhood	Fixed, slowly progressive, erythematous, hyperkeratotic plaques with sharp, figurate borders; on cheeks, over knees, elbows, extremities, and rarely trunk; palmoplantar keratoderma common		Nondiagnostic; acanthosis, hyperkeratosis, and prominent granular layer
Acral peeling skin syndrome	TGM5	AR		Recurrent spontaneous painless superficial peeling on dorsal hands and feet, followed by the development of mild erythema; resolves without scarring; exacerbated by heat and humidity		Separation occurs between the junction of the stratum granulosum and the stratum corneum

Continued

**Table 4-24.** Features of Selected Ichthyoses and Erythrokeratodermas—cont'd

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Congenital hemidysplasia with ichthyosiform erythroderma and limb defects ( <b>CHILD syndrome</b> (Fig. 4-38))	<i>NSDHL</i> (3β-hydroxysteroid dehydrogenase)	<b>XLD</b>	Birth	At birth, unilateral (right > left-sided) erythema and waxy, yellowish adherent scale on <b>1/2 of the body</b> (trunk/extremities); later, verrucous hyperkeratosis of variable extent, with affinity for skin folds	<b>Ipsilateral skeletal hemidysplasia</b> (hypoplastic limbs); <b>ipsilateral organ hypoplasia</b> ; ipsilateral alopecia; may also see stippled epiphyses/chondrodysplasia punctata (similar to Conradi-Hunermann-Happle)	Nonspecific; acanthosis, papillomatosis, and superficial perivascular infiltrate	Genetic testing
Conradi-Hunermann-Happle syndrome (X-linked dominant chondrodysplasia punctata) (Fig. 4-39)	<i>EBP</i> (emopamil-binding protein)	<b>XLD</b>	Birth	At birth, ichthyosiform erythroderma ( <b>generalized</b> , vs unilateral in CHILD syndrome) with feathery, adherent scale along Blaschko's lines; <b>erythema resolves</b> in first few months of life (unlike CHILD syndrome) and is replaced by follicular <b>atrophyderma</b> along Blaschko's lines, most prominently on the forearms and dorsal hands	Unilateral cataracts; <b>stippled epiphyses/chondrodysplasia punctata</b> seen only during infancy; asymmetric skeletal abnormalities, including scoliosis and rhizomelic limb shortening, but less severe than CHILD syndrome; frontal bossing w/ macrocephaly; patchy scarring alopecia	Nonspecific; hyperkeratosis and focal parakeratosis; may see dystrophic calcification in keratotic plugs	<b>Epiphyseal stippling on X-ray</b> only visible during infancy; accumulation of plasma cholesterol; genetic testing
Ichthyosis follicularis-atrichia-photophobia (IFAP) syndrome	<i>MBTPS2</i>	<b>XLR</b>	Birth	Erythroderma, scaling, and follicular hyperkeratosis; generalized alopecia, including eyebrows and eyelashes	Growth retardation and microcephaly; corneal opacities and ulcerations; photophobia; vascularizing keratitis; variable hearing loss; nail dystrophy; variable intellectual impairment, developmental delay, seizures, and structural CNS anomalies; genitourinary anomalies and skeletal anomalies	Follicular plugging and hypoplastic pilosebaceous structures	

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization

\*Also occasionally associated with CIE or intermediate LI/CIE phenotypes; a CIE-like phenotype is also seen in harlequin ichthyosis survivors.

†Also occasionally associated with mild LI or intermediate LI/CIE phenotypes.

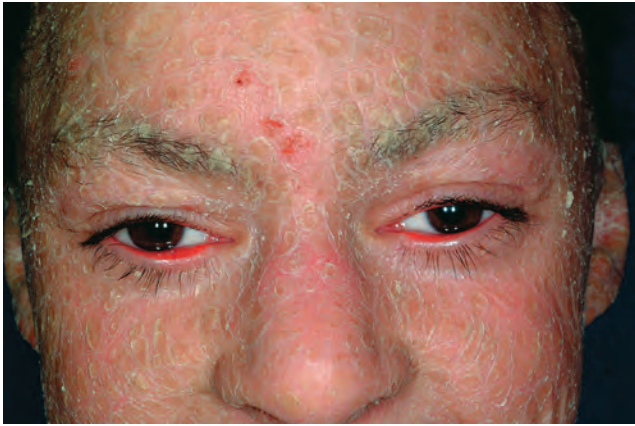
(Adapted from Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 4-25.** Selected Hereditary Palmoplantar Keratodermas (PPKs) With Known Genetic Basis

Type	Gene	Gene Product	Synonyms	Inheritance	Onset	Transgressions	Comments
<b>Diffuse</b>							
Unna-Thost (Fig. 4-40)	<b>KRT1</b> <i>KRT6c</i>	<b>Keratin 1</b> Keratin 6c	Nonepidermolytic PPK (NEPPK)	AD	2–5 years, sometimes later	No	Second most common type of diffuse PPK (after EPPK). Diffuse, well-demarcated PPK w/ yellow hue; hyperhidrosis. Histology w/ prominent orthokeratosis
Vörner	<i>KRT1</i> <i>KRT9</i>	Keratin 1 Keratin 9	Epidermolytic PPK (EPPK)	AD	0–3 years	No	<b>Clinically identical to diffuse NEPPK, but histology shows epidermolytic hyperkeratosis</b>
Mal de Meleda	<i>SLURP-1</i>	Secreted Ly6/Plaur domain-containing protein-1	Mal de Meleda	AR	0–3 years	Yes	Atopic dermatitis; <b>transgradiens</b> PPK erythematous w/ fissures/hyperhidrosis/maceration/ <b>horrible odor</b> /often infected; <b>dystrophic nails</b>
Greither	<i>KRT1</i> (in some families)	Keratin 1	Transgradiens and progrediens PPK	AD	Infancy	Yes	
Mutilating (Vohwinkel) (Fig. 4-41)	<i>LOR</i> (+ ichthyosis) <i>GJB2</i> (+ deafness)	Loricrin Connexin 26	Vohwinkel syndrome; keratoderma hereditaria mutilans	AD	Infancy	Yes	<b>Honeycombed palmar PPK, pseudoainhum</b> (esp. fifth finger – constriction bands → autoamputation), <b>starfish keratosis</b> on the knuckles/ feet/elbows/knees, linear keratosis on elbows/knees, <b>sensorineural deafness (Cx26)</b> , and generalized <b>ichthyosis (loricrin)</b>
Papillon-Lefèvre syndrome	<i>CTSC</i>	Cathepsin C	PPK with periodontitis	AR	Birth to early infancy	Yes, diffuse	<b>Transgradiens</b> PPK w/ erythema/hyperhidrosis/terrible odor (soles > palms); pyogenic infections; <b>periodontitis/gingivitis</b> → <b>premature loss of teeth</b> , psoriasiform lesions on elbows/knees, and pyogenic infections; <b>dural calcification</b>
Naxos disease	<i>JUP</i>	Plakoglobin	Diffuse NEPPK with woolly hair and cardiomyopathy	AR	Infancy	No	Woolly hair; arrhythmias and <b>right ventricular cardiomyopathy</b> develop during adolescence
<b>Focal</b>							
Striate type Areata type	<i>DSG1</i> <i>DSP</i> <i>KRT1</i> <i>KRT16</i> <i>KRT6c</i>	Desmoglein 1 Desmoplakin Keratin 1 Keratin 16 Keratin 6c	Wachters type, Brünauer-Fuhs-Siemens type	AD	4–10 years	No	Striate on palms and islands on feet; variable phenotype
Richner-Hanhart syndrome	<i>TAT</i>	<b>Tyrosine amino-transferase</b>	<b>Tyrosinemia type II</b> , oculocutaneous tyrosinemia	AR	Infancy (ocular) Early childhood to adolescence (skin)	No	<b>Focal painful PPK on weight-bearing areas; dendritic keratitis, corneal ulcers, and blindness</b> (ocular findings prior to skin findings); hyperkeratosis of elbows/knees; mental retardation
Pachyonychia congenita	<i>KRT16</i> <i>KRT6a</i> <i>KRT17</i> <i>KRT6b</i>	Keratin 16 Keratin 6a Keratin 17 Keratin 6b	PC1, Jadassohn-Lewandowsky type PC2, Jackson-Lawler type	AD	Infancy to early childhood	No	PC1: more severe NEPPK PC2: steatocystoma multiplex and eruptive vellus hair cysts more common; natal teeth
Carvajal syndrome	<i>DSP</i>	Desmoplakin	Striate PPK with woolly hair and cardiomyopathy	AR > AD	Infancy	No	Woolly hair; <b>dilated left ventricular cardiomyopathy</b> (variable onset); occasionally skin fragility, nail dystrophy, hypodontia
Howell-Evans syndrome	<i>RHBDF2/IRHOM2</i>	Rhomboid 5, drosophila, homolog of 2/inactive rhomboid protein 2	<b>Tylosis with esophageal cancer</b>	AD	Childhood	No	<b>Thick yellow PPK on weight-bearing areas</b> (heels and balls of feet) starting in second decade <b>Significant risk for development of esophageal cancer in third to fifth decade</b>

AD, autosomal dominant; AR, autosomal recessive; SCC, squamous cell carcinoma (Adapted from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. 3rd Ed. Elsevier. 2012)





**Figure 4-36.** Lamellar ichthyosis phenotype of ARCI. Large plate-like scaling on the forehead and cheeks. This patient shows moderate ectropion. (From Paller S, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 4th Ed. Elsevier. 2011)



**Figure 4-37.** Erythroderma, hypotrichosis, and areas with ichthyosis linearis circumflexa. (From *Allergology and Immunopathology [Allergologia et Immunopathologia]*. Serena Pastore, Gaia Gorlato, Irene Berti, Egidio Barbi, Alessandro Ventura Volume 40, Issue 5. Pages 316-317. Elsevier. 2012)



**Figure 4-38.** CHILD Syndrome. Unilateral erythema and scale with ipsilateral limb defects. (Rimoin D, Michael Connor J, Pyeritz R, Korf B. *Emery and Rimoin's Principles and Practice of Medical Genetics e-dition*, 5th Ed. Elsevier. 2007.)



**Figure 4-40.** Unna-Thost syndrome. (From Gehris, Robin P., Ferris, Laura K. *General Dermatology*. January 1, 2009. Pages 277-296)



**Figure 4-39** Conradi-Hünemann syndrome. **(A)** Thick, psoriasiform scaling overlying erythema in a 1-month-old girl with the syndrome and chondrodysplasia punctata. As the scaling desquamated, the underlying erythema along Blaschko's lines became more apparent. (Eichenfield L.F. et al. *Neonatal and Infant Dermatology* 3rd ed. Elsevier. 2015) **(B)** The pattern of scale along Blaschko's lines is more evident in this neonate with Conradi-Hünemann syndrome. (From Paller AS. *Ichthyosis in the neonate*. In: Dyall-Smith D, Marks R, eds. *Dermatology at the millennium: Overview of past achievements, current knowledge and future trends*. London: Parthenon Publishing Group; 1998, with permission.)



**Figure 4-41.** Vohwinkel's. Mutilating keratoderma. (From Gehris, Robin P.; Ferris, Laura K General Dermatology. January 1, 2009. Pages 277-296)

## 4.15 MISCELLANEOUS PEDIATRIC DERMATOLOGIC DISORDERS

### Hydroa vacciniforme

- Mean age = 8 years; equal sex ratio
- UVA is most common trigger, but mechanism unclear
  - Probable role of chronic or latent EBV infection
    - Associated with atypical hydroa vacciniforme or hydroa vacciniforme-like lymphoproliferative disorder
    - EBV also detected in lesional skin and blood of patients with classical hydroa vacciniforme
- Outbreaks typically occur only in **summer**; eruption begins within a few hours of sun exposure
- Most common on **face and dorsal hands**, but can occur on any sun-exposed area
- Starts with burning or itching sensation that may be associated with mild constitutional symptoms
- Primary lesion is a pink macule or papule that progresses to vesicles and crusted erosions
- **Lesions resolve, resolve leaving punched out varioliform scars**
- Ocular involvement: photophobia, keratoconjunctivitis, or uveitis
- Histology: dense perivascular infiltrate composed of lymphohistiocytes and neutrophils
  - The epidermis is **edematous** with reticular degeneration and necrotic keratinocytes
  - Dermal vessels may demonstrate thrombosis or hemorrhage
- Photoprovocation testing with **UVA** can be performed to help confirm diagnosis
- **Children with severe or atypical cutaneous involvement or constitutional symptoms of fever, lymphadenopathy, and hepatosplenomegaly should be evaluated for a concomitant EBV-associated lymphoproliferative disorder**

- Treatment: sun avoidance/photoprotection, narrowband UVB phototherapy in the spring to "harden" skin; hydroxychloroquine, beta-carotene, thalidomide, azathioprine, and cyclosporine may help
- **Usually resolves during adolescence or young adulthood**

### Actinic prurigo

- Most common in **Native American** children; female > male; onset <10 years of age
- Caused by UVR (**esp. UVA**)
- May be an AD inheritance pattern with incomplete penetrance
  - **HLA-DR4 DRB1\*0407 polymorphism present in 60%–70% of patients**
- Seasonal variability in severity
  - **Flares in spring and persists through summer**
  - Improves in fall, but usually **does not completely remit in winter**
- Intensely pruritic eruption on sun-exposed areas, though covered skin may also be involved
  - Presents as papules and nodules that are frequently excoriated and crusted
  - Progresses to eczematous plaques with lichenification; secondary bacterial infection may occur
  - Dyspigmentation and scarring are common (versus PMLE)
- **Actinic cheilitis is a characteristic feature**
  - 65%–85% of patients will have lip involvement with pruritus, edema, scale, and crusting
  - Actinic cheilitis without other features may be seen in 10%–25% of children
- **Actinic conjunctivitis** can manifest as epiphora and photophobia
- Biopsy of the lips commonly shows lymphoid follicle formation and is a distinguishing feature
- Phototesting shows ↓MED in 60%
- Treatments: sun avoidance/photoprotection, narrowband UVB phototherapy in the spring can minimize flares, topical corticosteroids, and short courses of oral prednisone may help with flares; mainstay of treatment is **thalidomide**
- Often has a **chronic course** that continues into adulthood

### Juvenile spring eruption

- **Boys > girls**; 5–12 years of age
- Triggered by UVA, UVB, and rarely visible light
- Thought to be a **variant of PMLE**
- Occurs in **early spring** with improvement through the season
- Pruritic, skin-colored to pink edematous papules that can progress to vesicles and crusting
  - Most common on the **helical ears**, but can affect the hands or face
  - Lesions self-resolve in 1 week w/o scarring
- Treatment: sun avoidance and photoprotection; narrowband UVB phototherapy for a 4- to 6-week course



at the beginning of spring may prevent recurrence; topical and systemic corticosteroids; oral antihistamines

- Lesions self-resolve in several weeks, but may recur each spring; disease remits after puberty

### Diaper dermatitis

- Peak incidence at 9–12 mos
- Risk factors: contact with urine/feces, friction/maceration, and 2° infection with bacteria and/or yeast
- Irritant contact dermatitis: erythema of convex surfaces, but tends to spare the folds
- **Candidiasis**: beefy red erythema and pustulovesicular “satellite” lesions
- **Granuloma gluteale infantum**: purple red nodules, often appearing after use of topical steroids
- **Perianal pseudoverrucous papules and nodules**: flat topped, wart-like papules and nodules appear in incontinent patients as a form of severe irritant contact dermatitis
- **Jacquet’s erosive dermatitis**: severe erosive dermatitis with ulcerated papules and nodules
- Treatment:
  - Meticulous diaper hygiene with frequent diaper changes and gentle cleansing
  - Application of thick barrier ointments
  - Low potency topical steroid ointments (**avoid in granuloma gluteale infantum**)

### Juvenile plantar dermatosis

- Boys > girls
- May be worse in summer and cold weather
- Most likely represents a **frictional irritant dermatitis**
- Erythematous, symmetrical, **smooth** red plaques, affecting the **plantar surfaces** of the distal soles and toes, with sparing of the web spaces
  - 5% may have similar changes on fingertips
  - May be associated with hyperhidrosis (“**sweaty sock syndrome**”)
- Treatments: cotton or super absorbent socks and avoidance of occlusive footwear, absorbent foot powder, emollients, and medium-/high-potency topical corticosteroids

### Acropustulosis of infancy

- Onset is typically between birth and 2 years of age
  - Most common in **black infants**
- Etiology unknown; some cases a/w **preceding scabies** infection
- Recurrent crops of vesiculopustules over the **palms, soles, and distal extremities**
- Treatment: systemic antihistamines and high potency topical corticosteroids
- Typically resolves spontaneously by 3 years of age

### Cutaneous findings in patients with chromosomal abnormalities

- Down syndrome (trisomy 21): transverse palmar crease, **syringomas**, **elastosis perforans serpiginosa**, alopecia areata, epicanthic folds, and scrotal tongue
- Turner syndrome (XO): **cystic hygroma** → webbed neck, multiple nevi, propensity towards keloid formation, nail dystrophy, and low posterior hairline
- Noonan syndrome: lower extremity lymphedema, CALM, multiple nevi, light/curly/rough hair, hypertelorism, **ulerythema ophryogenes**, webbed neck, lowered nuchal hairline, and low set ears (**note: allelic with LEOPARD syndrome – both have pulmonic stenosis**)
- Klinefelter syndrome (XXY): ↑varicosities, **leg ulcers**, ↓body hair, marfanoid habitus, and gynecomastia

### Cutaneous mastocytosis

- Childhood and adulthood types; most cases present before 15 years of age
- Adults more likely than children to develop systemic symptoms/disease
- **c-KIT mutations** (activating mutations typically)
  - D816V activating mutation found in 42% of children and adults
- Of note, *c-KIT* encodes KIT (CD117) on mast cells; stem cell factor is the ligand for KIT and essential for survival of mast cells
- Childhood forms
  - **Solitary mastocytoma**
    - Usually occurs as single tan/yellow-tan plaque/nodule
    - Most commonly seen on distal extremities
    - Generally self-resolves over 1–3 years
  - **Urticaria pigmentosa/maculopapular mastocytosis** ([Fig. 4-42](#))
    - **Most common presentation in children**
    - Multiple light brown to red-brown macules and papules, which can occur anywhere; start on trunk; spare palms/soles/face
    - Pruritus and flushing may be seen; blistering (bullous mastocytosis) in about 1/4 patients
    - Symptoms improve by early adolescence, but skin lesions may not completely resolve
    - Patients with more lesions are more likely to have systemic symptoms
      - ◆ Diarrhea, abdominal pain, and wheezing/dyspnea are most common symptoms
      - ◆ Anaphylaxis is rare, but possible
  - **Diffuse cutaneous mastocytosis**
    - Infiltrated, red-brown, leathery plaques with **peau d’orange** appearance that can involve large areas of body
    - Skin lesions frequently blister → erosions
    - ↑incidence of systemic symptoms and progression to systemic mastocytosis
    - Can also occur in adults, although rarely



**Figure 4-42.** Multiple tan to brown lesions of urticaria pigmentosa. (From Callen JP, et al. *Dermatological Signs of Internal Disease* 4th ed. Elsevier. 2009)

- **Adult forms**
  - Reddish-brown macules/papules: occur on trunk/proximal extremities; ↑ in # over time; hyperpigmented; **most common presentation in adults**
  - Telangiectasia macularis eruptive perstans: telangiectatic macules and patches with no hyperpigmentation
- **Darier's sign** (local erythema or urticarial wheal after friction or rubbing) is present in all forms
- Systemic manifestations commonly occur in the systemic mastocytoses (e.g., indolent systemic mastocytosis, mast cell leukemia, and aggressive systemic mastocytosis)
  - Prognosis is poor for many of these disorders
  - Symptoms include skeletal lesions, bone marrow involvement, hepatosplenomegaly, lymphadenopathy, GI symptoms (diarrhea, abdominal pain, nausea/vomiting, and GI hemorrhage), and mixed organic brain syndrome
- On histology, mast cell infiltrates are seen in the dermis of lesional skin
  - Eosinophils and hyperpigmentation of the basal layer may be present
  - Stains: **toluidine blue, Giemsa, Leder, tryptase, and CD117 (kit) antibodies**
  - Bone marrow biopsy should be performed when considering systemic disease
- **Serum tryptase may be elevated** but is often normal; urinary histamine and histamine metabolites (1,4-methylimidazole acetic acid and N-methylimidazoleacetic acid) may be detectable
- Treatment:
  - Avoid mast cell degranulators (e.g., alcohol, anticholinergics, NSAIDs, aspirin, narcotics, polymyxin, and systemic anesthetics)

- Antihistamines (H1 and H2 antagonists), topical/systemic steroids, topical calcineurin inhibitors, oral cromolyn, PUVA/UVA1, intramuscular epinephrine, and imatinib (**in some with systemic mastocytosis – e.g., those who have *FIP1L1-PDGFR* gene rearrangement**)

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# 5

## Infectious Diseases

*Ali Alikhan and Thomas Hocker*

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### 5.1 VIRAL DISEASES

#### I. Human papillomavirus (HPV)

- **Double-stranded DNA virus** that infects skin and mucosal epithelial cells → **warts** and malignancies (e.g., **cervical cancer** and **SCC**)
  - **Capsid**
    - Contains DNA
    - Composed of L1 (major structural protein) and L2 (minor structural protein) – important for binding/entering epithelial cells
  - HPV is species-specific and requires fully differentiated squamous epithelia for its life cycle
    - Productive infection/hyperproliferation can only be accomplished if virus infects basal layer keratinocytes; early proteins (E1-E7) are responsible for **DNA replication** and keratinocyte immortalization; late proteins (L1-L2) are expressed in superficial epidermis and encode **structural proteins** required for virion formation
    - E1 and E2 genes are first to be expressed at stratum basale and spinosum – control transcription of other genes + replication of viral DNA (using host cell machinery)
    - E4 protein disrupts cytokeratin network → koilocytosis
    - E5, E6, and E7 genes allow viral replication above stratum basale → **amplification**
      - ◆ E6 and E7 decrease host immune response (e.g., TLR9 and IL-8)
      - ◆ **E6 and E7 in high-risk mucosal subtypes are oncoproteins**
        - E6 → ubiquitin-mediated p53 destruction → ↓apoptosis/↑replication/↑mutations
        - E7 binds RB → loss of inhibition of E2F transcription factor → ↑expression of genes important for DNA replication
- More superficial epidermal layers have higher L1 and L2 levels; **complete virus observed in granular layer and above**
- Host response is primarily cell-mediated in nature, along with help from the innate immune system (e.g., TLR-3 and TLR-9)
- Genus **α** (most of the mucosal and cutaneous HPV types) and **β** (epidermodysplasia verruciformis (EV)-associated HPV types) account for most known types
- Typically spread via sexual contact or skin-to-skin/fomite contact
- Most warts resolve in 1 to 2 years without treatment
- Cutaneous manifestations of HPV infection
  - Common warts: hyperkeratotic papules with pinpoint black dots (thrombosed capillaries), most commonly on fingers, dorsal hands/elbows/knees; usually **HPV-1, HPV-2, HPV-4, HPV-27, and HPV-57** (HPV-57 can cause 10 nail dystrophy)
  - Palmar/plantar warts: thick/deep endophytic papules with black dots on palms/soles
    - **Myrmecial** refers to anthill appearance of some plantar warts; **mosaic** refers to coalescence of several warts on plantar surfaces
    - **HPV-1, HPV-2, HPV-4, HPV-27, and HPV-57**
    - Histology: “**church spire**” papillomatosis + hyperkeratosis, acanthosis (with elongated rete ridges), **hypergranulosis**, and **koilocytosis** (granular layer); ↑dermal vessels
  - Flat/plane warts: light pink/brown, **soft/smooth**, slightly raised, occ. linear flat-topped papules on **dorsal hands/face**
    - More common in **children; adult women** >> adult men
    - **HPV-3, HPV-10, HPV-28, and HPV-41**

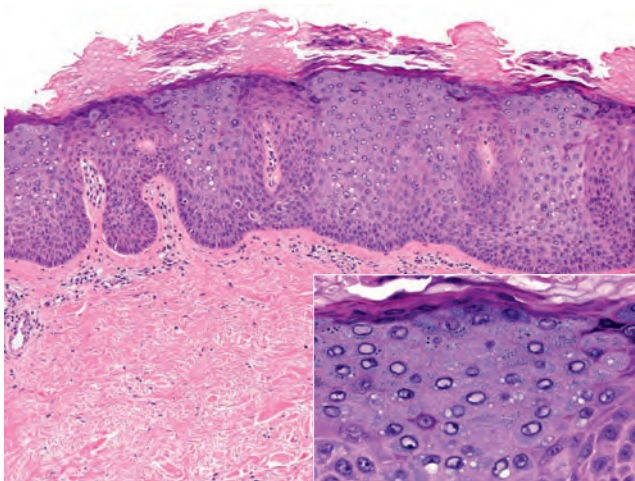


- Histology: orthokeratosis, mild papillomatosis, hypergranulosis, acanthosis, and koilocytosis (granular layer)
- Butchers warts: extensive lesions on hands in meat/fish-handlers; **HPV-7** and **HPV-2**
- Ridged warts retain normal dermatoglyphics – **HPV-60**; pigmented variant is more common in Japan
- Epidermodysplasia verruciformis: genetic disorder in which host has susceptibility to **genus  $\beta$  HPV types** (HPV-3, **HPV-5**, **HPV-8**, HPV-9, HPV-12, HPV-14, HPV-15, HPV-17, HPV-19, HPV-25, HPV-36, and HPV-38)
  - Autosomal recessive inheritance – mutations in TMC6 (**EVER1**) and TMC8 (**EVER2**)
  - **Acquired form may be seen in HIV**
  - HPV types 5 and 8 can → AKs and SCC (generally patients  $\geq 30$  years old in sun-exposed areas;  $>30\%$  of pts will develop SCC)
  - Generalized polymorphic papules (generally **flat wart-like appearance** (dorsal hands, neck, face, and extremities), but also **scaly, pink macules or hypopigmented, guttate macules/patches**, and seborrheic keratosis-like lesions on forehead/neck/trunk)
  - Some cases have extensive and confluent warts → generalized verrucosis
  - Histology: flat wart-like architecture + cells w/ perinuclear halos and **blue-gray granular cytoplasm** (Fig. 5-1)
- WHIM syndrome: autosomal dominant, 1° immunodeficiency caused by a CXCR4 mutation – warts, hypogammaglobulinemia, infections (bacterial), and neutropenia (2° to myelokathexis)
- WILD syndrome: warts, immunodeficiency, lymphedema, and dysplasia (anogenital)
- Treatments: destructive (cryotherapy, ED&C, scissors/shave removal, laser (PDL or CO<sub>2</sub>)/PDT, cantharidin, and salicylic acid preparations), immunomodulatory/

antiviral (SADE/DPCP and intralesional immunotherapy [e.g., *Candida*]), and 5-FU (topically w/ salicylic acid usually or intralesional), intralesional (bleomycin and cidofovir gel)

• Mucosal/Genital manifestations of HPV infection

- Genital warts (condyloma acuminata)
  - **Most common STD**
  - Occur on external genitals/perineum/perianal/groin/mons/vagina/urethra/anal canal
  - Smooth, sessile, raised, skin-colored to brown lobulated papules
  - **HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, and HPV-45**
  - Condylomata plana (flat cervical warts) best seen w/ **acetic acid** → **whitening**
  - Most cases resolve spontaneously within 2 years
  - RFs: sexual intercourse at young age, # of sexual partners, and MSM
  - Circumcision → ↓risk HPV transmission
  - May → **cervical cancer**
    - ◆ Most common scenario = persistent cervical infection with high-risk HPV type (**HPV-16, HPV-18, HPV-31, HPV-33, and HPV-45**)
    - ◆ Immunosuppression (e.g., HIV+) can ↑risk
  - Histology: epidermal hyperplasia, koilocytosis (should be seen in stratum spinosum too), papillomatosis (less severe and more rounded than in common warts), and parakeratosis
  - Treatments: destructive (cryotherapy, TCA (higher concentrations), electrosurgery, scissors/shave removal, laser (CO<sub>2</sub>)/PDT, and podophyllotoxin/podophyllin), immunomodulatory/antiviral (imiquimod, sinecatechins, intralesional immunotherapy, and cidofovir gel/intralesional)
  - **HPV vaccines**: contain L1 major capsid protein (self-assembles into virus-like particles → allow for development of immunity without any harm because they do not contain DNA)
    - ◆ Three types: **quadrivalent** (Gardasil; HPV-6, HPV-11, HPV-16, and HPV-18), **bivalent** (Cervarix; HPV-16 and HPV-18), and **9-valent** (HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58)
    - ◆ Best to use before sexually active – FDA-approved for females and males 9 to 25/26 years old
- Bowenoid papulosis: multiple **brown papules/smooth plaques** on genitals/perineum/perianal that are high-grade squamous intraepithelial lesions (HSIL) or SCCIS; **progression to invasive SCC is very rare**; a/w **high-risk HPV types**
- Erythroplasia of Queyrat: **red smooth plaque** on glabrous penis/vulva that is HSIL or SCCIS; increased risk of **progression to invasive SCC**; has **high-risk HPV types**
- Buschke-Lowenstein tumor (arises on genitals)
  - Part of a group of **verrucous carcinomas** (slow growing and locally destructive) that includes **oral florid papillomatosis** (HPV-6, HPV-11; RFs: smoking, radiation, and inflammation), **epithelioma cuniculatum** (HPV-2, HPV-11, and HPV-16), and papillomatus cutis carcinoides



**Figure 5-1.** Histology of epidermodysplasia verruciformis. Note the cells with perinuclear halos and blue-gray granular cytoplasm in the mid to upper epidermis. (Courtesy, Lorenzo Cerroni, MD. *Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd edn. Elsevier, 2012.*)

- HPV-6 and HPV-11
- Cauliflower-like tumors that infiltrate deeply on external genitals and perianally
- Histology: papillomatous acanthotic epidermis with bulbous ("pushing") downward-extending rete ridges; no cellular atypia/basement membrane penetration
- Treatment: excision with clear margins
- Oral warts: soft pink-white papules on any oral surface; HPV-6 and HPV-11; more common in HIV
- Focal epithelial hyperplasia (**Heck's disease**): multiple flat wart-like papules on gingival/buccal/labial mucosa in children (esp. South American); HPV-13 and HPV-32
- Recurrent respiratory papillomatosis: papillomas of airways due to HPV-6 and HPV-11; #1 benign tumor of larynx; hoarseness + stridor + respiratory distress; childhood (2° to vertical transmission) and adulthood (2° to genital-to-oral contact) onsets; can → SCC, esp. in smokers

## II. Human herpes viruses

- A total of 8 distinct human herpesviruses (HHV-1 to HHV-8) belong to the *Herpesviridae* family; all are characterized by an icosahedral capsid containing **linear double-stranded DNA**, surrounded by a glycoprotein-containing envelope; **replicate in host nucleus**
- Pathogenesis involves infection, latency, and reactivation

### Herpes simplex virus (HHV-1/HSV-1 and HHV-2/HSV-2)

- Recurrent vesicular eruptions occurring in **orolabial** (classically HSV-1) and **genital** (classically HSV-2) regions
- Primary infection = first infection with virus (may → symptoms); latency = virus **lies dormant in sensory (dorsal root) ganglia**; reactivation/recurrence (may → symptoms)
- Genital herpes RFs: 15 to 30 years old, ↑sexual partners, lower income/education, **HIV(+)** (vice versa too – genital HSV-2 → ↑HIV risk), and homosexuality
- **Pathogenesis**
  - Infection can occur without clinical lesions (and often does), and virus may still be shed
  - HSV-1 spread by saliva/secretions and HSV-2 spread by sexual contact → viral replication at skin/mucous membrane → retrograde axonal flow to dorsal root ganglia → latency and subsequent reactivation
  - HSV can evade host immune system (e.g., ↓expression of CD1a by APCs, ↓TLR signaling)
  - Reactivation triggers: **stress**, **UV** (UVB > UVA), fever, injury (e.g., **chemical peel or fractionated laser**), and immunosuppression
- **Clinical presentation**
  - Classic appearance: grouped/clustered vesicles on a **red base**
  - Can become pustules, erosions (with classic scalloped borders due to coalescence), and ulcers, ultimately crusting over and healing within 6 weeks

- 1° infection: 3 to 7 days postinfection → prodromal symptoms (tender lymphadenopathy, malaise, anorexia, and fever) → mucocutaneous lesions +/- pain/tenderness/burning/tingling just before lesions erupt
- **Recurrent infections: generally milder than 1° infections**, have 24 hour prodrome of tingling/itch/burning
- Orolabial infection
  - 1° HSV can be severe (gingivostomatitis in children; pharyngitis/mononucleosis-like in adults)
  - Mouth (esp. buccal mucosa and gingivae; favors anterior mouth unlike herpangina) and lips (recurrent lesions prefer **vermillion border**) affected
- Genital herpes
  - 1° infection often asymptomatic, but can → **painful/tender erosions** on external genitalia, vagina, cervix, buttocks, and perineum (women) +/- lymphadenopathy/dysuria (women mainly)
    - ◆ 1° worse in women – ↑% extragenital involvement, urinary retention, and aseptic meningitis (10%)
  - Recurrent – mildly symptomatic with few vesicles lasting about 1 week; frequency of outbreaks usually decreases over time
- Other HSV presentations
  - **Eczema herpeticum**: widespread, sometimes severe HSV infection in areas of **atopic dermatitis**, Hailey-Hailey, or Darier's disease (**Fig. 5-2**) +/- **systemic symptoms**, lymphadenopathy, may be **life-threatening**; ↑in children
    - ◆ ↑with filaggrin mutations
    - ◆ **Usually HSV-1**; associated with Th2 shift in immune system
    - ◆ ↑in patients with severe atopic dermatitis w/ onset <5 years old, ↑IgE levels, ↑eosinophils, and food/environmental allergies



**Figure 5-2.** Eczema herpeticum. Monomorphic, punched-out erosions with a scalloped border in this infant with a history of facial atopic dermatitis. (Courtesy, Julie V Schaffer, MD. Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

- ◆ Have been associated with topical calcineurin inhibitors
- Herpetic whitlow: infection of **digits (HSV-1 in children and HSV-2 in adults)** w/ vesiculation/pain/swelling; recurrence seen; bimodal peaks at <10 years old and 20 to 40 years old
- Herpes gladiatorum: HSV-1 infection 2° to athletic contact (classically **on lateral neck/side of face and forearm**)
- HSV folliculitis (herpetic syphilis): follicle-based vesicles/pustules in beard-area (HSV-1)
- Severe/chronic HSV: large, chronic ulcers may involve respiratory or GI tract; more common in immunocompromised
- Ocular HSV: keratoconjunctivitis w/ lymphadenopathy and **branching dendritic corneal ulcer**; blindness may occur (HSV-2 in newborns; HSV-1 otherwise)
- **HSV encephalitis**: most common fatal viral encephalitis in the United States (>70% die without tx); can be associated with mutations in TLR-3 or UNC-93B; usually **HSV-1**; fever/altered mentation/strange behavior; **temporal lobe #1 site**
- Neonatal HSV– see Pediatric Dermatology section
- **Diagnosis**
  - Viral culture (high specificity, low sensitivity), direct fluorescent antibody assays, serology (Western blot = gold standard), **PCR (most sensitive/specific)**, and **Tzanck smear** (multinucleated epithelial giant cells; best when done on acute lesions)
  - Histology: intraepidermal vesicle + slate-gray enlarged keratinocytes (ballooning degeneration) which are **multinucleated with margination of chromatin**
    - +/- Cowdry A inclusions (eosinophilic inclusion bodies) within nucleus, epidermal necrosis, multicellular dermal infiltrate, and perivascular cuffing
- **Treatment**
  - Orolabial: oral penciclovir/valacyclovir, topical penciclovir, or topical acyclovir/hydrocortisone combination
  - Genital: oral acyclovir/famciclovir/valacyclovir
    - Use meds w/in first 48 hours → ↓pain/healing time/viral shedding
    - Suppressive daily doses may be given in patients with >6 outbreaks of orolabial/genital HSV per year (also ↓viral shedding)
  - May need **IV acyclovir in eczema herpeticum, neonatal HSV, or severe HSV in immunosuppressed**
  - **Foscarnet or cidofovir for acyclovir-resistant HSV** (more common in immunosuppressed patients)
- Boards factoid: **HSV-1** is the most common cause of **EM minor** (herpes associated EM; HAEM)

### Varicella zoster virus (HHV-3)

- Causes varicella (chickenpox) and herpes zoster (shingles)
- Varicella is the 1° infection and herpes zoster is the reactivation of the latent infection (more common in **immunosuppressed and elderly** and can → death, e.g., via SIADH development in disseminated zoster patients)

- **Primary varicella incidence has decreased because of VZV vaccination**
- Herpes zoster occurs in 20% of adults, 50% of immunocompromised
  - Elderly at highest risk
  - RFs: physical and emotional stress, fever, trauma, and immunosuppression
  - Whites > nonwhites
- **Pathogenesis**
  - Transmitted via aerosolized droplets and direct contact with lesional fluid
    - Contagious from 1 to 2 days before lesion develops in varicella until all lesions crusted over
  - After primary varicella infection, **VZV travels to dorsal root ganglion and stays dormant** – if reactivated later will replicate, travel down sensory nerve to the skin, and present as herpes zoster
- **Clinical presentation**
  - Primary varicella
    - Primarily self-limited in healthy individuals
      - ◆ **More severe disease in adolescents and adults**
    - Prodromal symptoms: fever, fatigue, and myalgias
    - Cephalocaudal progression of classic lesions described as “**dew drops on rose petal**”: vesicles on an erythematous base that become pustular, then crust over
      - ◆ Crops of lesions in **various stages**
    - Vaccine-associated varicella zoster may rarely develop after the vaccine is administered – represents mild case of chickenpox that may start at injection site
    - Primary varicella in pregnancy
      - ◆ **Congenital varicella syndrome**: cutaneous scarring; CNS/ocular/limb anomalies; risk greatest if infection occurs during **first 20 weeks of gestation**; exposed fetus may develop reactivation (herpes zoster) in childhood
      - ◆ **Neonatal varicella**: perinatal varicella transmission (within **5 days before delivery until 2 days postdelivery**); disease is severe (up to **30% mortality**) because of the lack of protective maternal antibodies
  - Herpes zoster: prodrome (itch, tingling, hyperesthesia, and pain) → painful grouped vesicles on red base in a **dermatomal pattern**
    - **Trunk = most common location** (thoracic); face #2 (cranial; trigeminal nerve most common nerve involved); lumbar #3, and sacral #4
    - Postherpetic neuralgia: pain, potentially chronic, after lesions have cleared; **more common, severe and chronic in elderly**
    - In HIV patients, lesions more persistent and thickened
    - Disseminated disease = dermatomal disease + >20 **lesions outside of dermatome** +/- visceral involvement; almost exclusively seen in **immunosuppressed** (AIDS, lymphoreticular malignancy, long-term immunosuppressive



- medication use, etc.); increased risk of **life-threatening pneumonitis and encephalitis**
- Vasculopathies (usually of CNS, but also peripheral arteries) are a worrisome delayed complication
- **Dermatomal-specific herpes zoster findings:**
  - ◆ Ramsay-Hunt syndrome: disease of **geniculate ganglion** of facial nerve (CN-VII) may → ear pain, vesicles on tympanic membrane and EAM; **ipsilateral facial nerve paralysis**, dry mouth/eyes, **anterior 2/3 tongue taste loss**, and auditory (e.g., **deafness and tinnitus**) and equilibrium issues (vestibulocochlear nerve)
  - ◆ Aseptic meningitis and/or vasculopathy (encephalitis) if CN-V affected
  - ◆ Hearing impairment/deafness if CN-VIII affected
  - ◆ Eye involvement (**herpes zoster ophthalmicus**) if CN-II, CN-III, or CN-V affected
    - **Hutchinson's sign** (involvement of the side and tip of nose): indicates disease of the **external division of the V1 nasociliary branch**; may → to ocular involvement (e.g., keratitis, **uveitis**, acute retinal necrosis, and **visual loss**) 3/4 of time
    - Uveitis is most common form of ocular involvement; keratitis #2
  - ◆ **Bell's palsy** if CN-VII affected
  - ◆ Back dermatome complications
    - Cervical: motor neuropathy of arm (with possible atrophy) and diaphragm weakness
    - Thoracic: abdominal wall pseudohernia and weakness of muscles
    - Lumbar: motor neuropathy of leg (with possible atrophy)
  - ◆ Possible urinary hesitancy/retention if sacral dermatomes involved
  - ◆ Possible dilatation, constipation, pseudo-obstruction, reduced anal sphincter tone w/ thoracic/lumbar/sacral zoster
- **Diagnosis:** Tzanck smear, DFA, **PCR (sensitive, fast)**, viral culture (specific, not sensitive), serology (four-fold increase in IgG titer can retrospectively confirm prior infection), and skin biopsy (similar appearance to HSV, but immunohistochemistry can differentiate)
- **Treatment**
  - Primary varicella
    - Treatment with systemic acyclovir or valacyclovir **within 3 days of lesion onset** → ↓severity/duration disease
      - ◆ Oral administration appropriate in healthy children/adults
      - ◆ IV acyclovir in immunocompromised patients
    - Post-exposure prophylaxis
      - ◆ Varicella vaccine may be given within 72 to 120 hours of exposure in nonimmune, immunocompetent individuals >12 months
      - ◆ VZIg (Varicella zoster immunoglobulin) should be administered within 96 hours of exposure in immunocompromised, pregnant females, and neonates
        - IVIg may alternatively be administered
  - ◆ Oral acyclovir can be administered within 7 to 10 days of exposure
  - Primary prevention = varicella vaccination
    - ◆ Live attenuated virus recommended as a 2 dose vaccination series; part of primary immunization series
    - ◆ Initial dose at 12 to 15 months, booster dose at 4 to 6 years
    - ◆ **Contraindicated in pregnancy and in immunocompromised patients**
  - Sequelae of primary varicella
    - ◆ **Reye's syndrome** in setting of aspirin administration (now rare)
    - ◆ **Pneumonia more common in older individuals**; high mortality if untreated
    - ◆ Encephalitis, cerebella ataxia, and hepatitis
  - Herpes zoster
    - **Antiviral treatment** with acyclovir (IV form in immunosuppressed), famciclovir, or valacyclovir is best given within 72 hours; prednisone helps with acute pain but has no effect on course or development of PHN
      - ◆ ↓duration of lesions/pain
      - ◆ ↓rate of postherpetic neuralgia (PHN) in patients >50 years old
      - ◆ Valacyclovir and famciclovir preferable to acyclovir
    - PHN: tricyclic antidepressants (e.g., nortriptyline), gabapentin, 8% capsaicin patch, pregabalin, opioid analgesics, and lidocaine patch
    - **Live attenuated vaccine** → ≈50%↓ in development of disease and 67%↓ in PHN; for immunocompetent patients >60 years old

## Epstein-Barr virus (HHV-4)

- Causes **infectious mononucleosis** plus many other disorders (e.g., **oral hairy leukoplakia**, hydroa vacciniforme, **Gianotti-Crosti syndrome**, genital ulcers, and various hematologic disorders/malignancies (e.g., **Burkitt's lymphoma**, NK/T-cell lymphoma, post-transplant lymphoproliferative disorder, and **nasopharyngeal carcinoma**)
- Pathogenesis: transmission via saliva/blood → infects mucosal epithelial cells initially → **B-cells** (where virus can lay dormant and evade immune system via production of EBNA-1 protein and latent membrane protein-2)
  - Incubation period of 1 to 2 months; symptoms develop with viral replication
  - **In patients with ↓cell-mediated immunity, infected B-cells may continue to replicate** → **lymphoproliferative disorders** (cell-mediated immunity appears to be more important than humoral, conferring immunity after first mononucleosis episode)
- Clinical features
  - Mononucleosis: typically **young adults w/ pharyngitis**, fever, and **cervical lymphadenopathy**
    - **Splenomegaly** (and possible rupture)
      - +/- hepatomegaly



- ↑LFTs in subset of patients
- **Lymphocytosis** (up to 40% atypical lymphocytes)
- May have nondistinct polymorphous (e.g., urticarial, morbilliform) eruption in 5% to 10% occurring within first week of illness
  - ◆ Centrifugal spread
  - ◆ Petechial lesions on eyelid and hard/soft palate junction
  - ◆ +/- genital ulcers (esp. females)
- Ampicillin/amoxicillin → “hypersensitivity” skin reaction (itchy generalized morbilliform eruption → desquamation)
- **Oral hairy leukoplakia**: corrugated white plaque typically on lateral tongue, with strong HIV association; more common in smokers
- **Gianotti-Crosti syndrome** and papular-purpuric glove and stocking syndrome (more common w/ parvovirus B19, though) may occur in setting of EBV infection
- **Diagnosis**:
  - Monospot test: nonspecific, confirms presence of **IgM heterophilic antibodies** which are often present in EBV infection and may persist for months after infection; 85% of older children/adults are positive during second week of infection, but Monospot is **often negative in younger children**
  - EBV-specific antibodies: **higher sensitivity in younger children**; can be useful in determining current vs prior infection (Table 5-1)
    - VCA (viral capsid antigen) IgM/IgG, EA (early antigen) IgG, and EBNA IgG
  - CBC may reveal lymphocytosis with atypical lymphocytes and thrombocytopenia
  - Transaminitis may be present
  - Positive heterophilic antibody (>1:40) and >10% atypical lymphocytes suggests acute infection
  - PCR to EBV DNA may be performed from tissue or blood; RT-PCR available from lymphoid cells
- **Treatment**:
  - Supportive care
  - Oral corticosteroids may be considered for severe cases of tonsillitis
  - **Avoid contact sports** until splenomegaly resolves (risk for **splenic rupture**)
  - Rare sequelae: upper airway obstruction, aseptic meningitis, meningoencephalopathy, myocarditis, pericarditis, and renal failure

**Table 5-1.** Epstein-Barr Virus-Specific Serology Interpretation

<b>Viral Capsid Antigen (VCA)</b>				
Status	IgG	IgM	EA	EBNA
No past infection	–	–	–	–
Acute IM	+	+	±	–
Convalescent IM	+	±	±	±
Past infection	+	–	Low + or –	+
Reactivated/chronic	++	±	++	±

(From Paller S, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 4th Ed. Elsevier. 2011)

## Cytomegalovirus (HHV-5)

- Transmitted via body fluids, fomites, vertical transmission, **transplanted organs**, and hematopoietic stem cells
- Infects leukocytes → dissemination → various organs → latency
  - Most infections are **asymptomatic in healthy adults**; however, can cause **severe disease in utero (TORCH)**, or in **immunosuppressed/transplant patients (CMV retinitis/blindness, meningoencephalitis, pneumonitis, GI ulcers)**
  - After the 1° infection, **very low risk of reactivation, except for immunocompromised patients**
- Cutaneous features in adults
  - **Mononucleosis-like presentation** (e.g., sore throat, fever, lymphadenopathy, and hepatosplenomegaly) may be associated with nonspecific exanthem (e.g., morbilliform)
    - If ampicillin given → eruption (as in infectious mononucleosis)
  - **Recalcitrant ulcers of perineum or leg in HIV patients**; these patients may also get verrucous plaques, vesicles, and/or nodules
- Diagnosis via human fibroblast culture (gold standard), but faster methods include shell vial assay, PCR, and serologic testing; **histology of ulcers may show enlargement of endothelial cells with pathognomonic “owl’s eye” (intranuclear) inclusions**
- **Ganciclovir (IV)** and **valganciclovir (oral)** are first-line treatments

## HHV-6 (Roseola infantum, exanthem subitum, sixth disease)

- One of the most common viral exanthems of childhood (discussed in detail in Pediatric Dermatology chapter); up to 15% of infants may develop febrile seizures, but otherwise follows a generally benign course in healthy pts
  - 95% of pts are between 6 months to 3 years of age
- Virus remains latent in T cells for life → reactivation has been a/w **pityriasis rosea** (along with HHV-7) and **DRESS syndrome** (along with EBV, CMV and HHV-7)

## HHV-7

- Lymphotropic virus that shares significant homology with HHV-6 and may participate in co-infection w/ HHV-6
- Although not definitively causative of any disease, it has been a/w **pityriasis rosea** (along with HHV-6), and a subset of exanthem subitum cases (co-infection with HHV-6; unique clinical presentation)

## HHV-8

- Etiologic factor for **Kaposi sarcoma** – discussed in Neoplastic Dermatology chapter
- Also associated with **multicentric Castlemann disease**, **primary effusion lymphoma (PEL)**, and paraneoplastic pemphigus

### III. Other viruses not covered elsewhere

#### Poxviruses

- **Smallpox** (*Variola virus*; *Orthopox* genus)
  - Infection via **respiratory tract** → 7 to 17 days incubation period → 1 to 4 days prodromal period (fever, headache, myalgias, and malaise) → **centrifugal** (face/arms/legs > trunk) vesiculopustular eruption and may involve hands/feet (lesions in any given anatomic region will be in **same stage**) w/ lethargic/"toxic" appearance
    - Rash: macule → papule → vesicle → **pustules**; **typically scarring**
    - Lesions **first appear on palms/soles**
    - Patients infectious from eruption onset till 7 to 10 days posteruption
    - Oral lesions (tongue, mouth, and oropharynx) often appear before cutaneous by **lesions** 1 day
  - Complications: blindness, **encephalitis**, toxemia, hypotension, pneumonitis, arthritis, and osteitis
  - Diagnosis: PCR, viral culture
  - Treatment: supportive; vaccine as prophylaxis
- **Vaccinia** (*Vaccinia virus*; genus = *Orthopox*): used for **live smallpox vaccine**
  - SEs: lymphadenopathy, ocular vaccinia, generalized vaccinia, vesiculopustular/urticarial/morbilliform eruption, **eczema vaccinatum** (in patients with **atopic dermatitis**, Darier's, or Hailey-Hailey disease), erythema multiforme, postvaccinal CNS disease, and progressive vaccinia (immunosuppressed patients; can → death)
- **Monkeypox** (*Monkeypox virus*; genus = *Orthopox*): central/western Africa, though United States outbreak from **prairie dogs**
  - Can spread via cutaneous inoculation or inhalation (hosts are monkeys, rodents, or humans)
  - Prodrome (fever/sweating/chills) → smallpox-like lesions, but usually milder/fewer lesions
    - Lesions may present in various stages and favor face and extremities (esp. **palms/soles**), with centrifugal spread; may scar
    - May have systemic symptoms (respiratory, fever, and LAD in 67%)
- **Cowpox** (*Cowpox virus*; genus = *Orthopox*): Europe and Asia
  - Spread via cutaneous contact (hands and face) with infected animal (**usually cats**)
    - Incubates 7 days → painful red papule at contact site → vesicular → pustular → hemorrhagic → ulcer w/ eschar
    - Lesions usually solitary and occur on hands/fingers
    - Can have LAD, and fever
- **Orf** (*ecthyma contagiosum*; *Orf virus*; genus = *Parapox*): as a result of contact with infected animals (**sheep, goats, or reindeer**; usually on udders/perioral areas of ewes)
  - Develop one to few lesions at contact site (usually hands)
- RFs: certain jobs (**shepherds, butchers, and veterinarians**)
- **Six lesion stages**: maculopapular (umbilicated) → targetoid → acute (weeping nodule) → regenerative (nodule w/ thin crust and black dots) → papillomatous → regressive (crust overlying resolving lesion)
- Self-resolves
- Diagnosis via histology (depends on stage) or PCR
- **Milker's nodules** ("*Pseudocowpox*"; *Paravaccinia virus*; genus = *Parapox*): papules at site of contact (**usually muzzles of calves and teats of cows**)
  - Distal upper extremities usually with single lesion(s), which look like orf
  - Most common in farmers/ranchers, veterinarians, and butchers
  - Diagnosis via histology or PCR
  - **Molluscum contagiosum** (*Molluscum contagiosum virus* [MCV]; genus = *Molluscipox*)
    - Common infection in **school-aged children**; may be sexually transmitted in adolescents/adults
    - Cause by molluscipox infection
      - Two subtypes: **MCV-I and MCV-II**
    - Infection spread by contact with infected skin or fomites, or possibly via water
    - Prototypical lesion is an **umbilicated, pink, and pearly papule**
      - Most common distribution: intertriginous areas, torso, lower extremities, and buttocks
      - Lesions can become widespread in patients with impaired skin barrier (atopic dermatitis or ichthyosis) or immunodeficiency (chemotherapy-induced or HIV; may also see **giant molluscum** lesions)
    - Histology: **molluscum bodies** within dermis
    - Treatments: cryotherapy, cantharidin, extraction/curettage, cimetidine, candida antigen immunotherapy, topical retinoids, and imiquimod
    - **Self-limited** with resolution after weeks to years of infection

#### Chikungunya virus

- Single-stranded (+)sense RNA virus belonging to *Togaviridae* family; classified as an "arbovirus" because has arthropod vector
- Transmitted by *Aedes* (*A. aegypti* > *A. albopictus*) mosquitoes; endemic to Africa/India/Southeast Asia
- Symptoms: **high fever, marked joint symptoms**, ("Chikungunya" is an African word for "crooked/bent joints") neuropathic acral findings, and headache/nausea/vomiting
- Cutaneous presentation: → **morbilliform eruption** (50%–75% of pts), mucosal aphthous-like ulcers, postinflammatory pigmentation of face/extremities, acral/facial edema, bullous eruptions in infants, and ecchymoses

#### Zika virus

- Icosahedral, single-stranded RNA virus within the *Flaviviridae* family

- Flaviviridae family includes Yellow fever, Dengue fever, Japanese encephalitis, West Nile virus, and Zika virus
  - All are termed “arboviruses” because they are viruses that are transmitted by arthropods (mosquitoes or ticks most commonly)
  - Review the excellent JAAD 2016 CME article by Nawas et al, *Emerging infectious diseases with cutaneous manifestations*
- Most commonly transmitted via bites from infected *Aedes aegypti* and *Aedes albopictus* mosquitos
  - Virus may also be transmitted via blood transfusions, **sexual contact**, and most importantly, **vertically (from mother to fetus) during pregnancy** → **microcephaly** and other fetal anomalies
- In 2016, the WHO classified Zika as a global threat and the CDC raised issued their highest alert due to Zika’s association with **microcephaly** and possible a/w **Guillain-Barré syndrome**
- Clinical features:
  - No gender or age predilection
  - Incubation period of 3–12 days → 20% of infected adults develop mild symptoms lasting up to 1-2 weeks
    - Systemic symptoms: fever, myalgia, arthralgia, headache, and conjunctivitis
    - Mucocutaneous symptoms:
      - ◆ **Nonspecific, diffuse morbilliform/scarlatiniform eruption** (begins 3 to 12 days after initial infection w/cephalocaudal progression; **starts on face** → spreads to trunk/extremities) → rash begins to subside after 3 days and completely resolves within 1 week of onset, sometimes with desquamation
      - ◆ Mild hemorrhagic manifestations (petechiae and bleeding gums)
  - Unfortunately, there are **no unique clinical features** to differentiate Zika from other arbovirus infections → must consider dengue and chikungunya infection in your differential diagnosis
- Diagnosis:
  - Confirmed with **RT-PCR** or **ELISA** during initial phase (first 7 days) of infection
    - Later in disease course, may check Zika-specific IgM antibodies and plaque reduction neutralization tests
- Treatment:
  - Currently no vaccine exists, and no specific anti-viral therapies are available; avoid aspirin and NSAIDs (can worsen hemorrhagic sequelae)
- **Prevention is critical!**
  - People traveling to endemic areas should wear long-sleeved shirts and pants, stay in cool rooms that have screens on windows and doors, and use insect repellents (DEET); **pregnant women should avoid travel to Zika-endemic areas!**

## Dengue virus

- Like Zika, West Nile virus and Yellow fever, Dengue is an arbovirus in the **Flaviviridae** family; also transmitted by *Aedes aegypti* mosquitoes
- Wide range of clinical presentations:
  - Asymptomatic infection: **most common** presentation (75% of cases)
  - Mild Dengue: very nonspecific, mimicking any other viral infection
  - Classic Dengue fever: fever, diffuse **morbilliform/scarlatiniform rash (50% of cases)**, **severe headache/myalgia/arthralgia**, retroorbital pain, +/- **petechial mucosal lesions**, epistaxis and gingival bleeding
    - Classic Dengue fever rash: widespread erythema with characteristic **white islands of sparing** → heals with desquamation
  - Dengue hemorrhagic fever (DHF): **more severe** than classic Dengue fever; most likely to develop when a patient **previously infected with 1 serotype is subsequently infected with a different viral serotype**
    - Most common in **children** younger than 15yo
    - Symptoms: lethargy/weakness, vomiting, facial flushing, and circumoral cyanosis
- Diagnosis:
  - Confirmed with **RT-PCR** or **ELISA** during initial/acute phase of disease, or IgM serologies later in disease course
  - Neutropenia helps distinguish from Chikungunya virus
- Treatment: No specific treatment; mainly supportive; avoid aspirin and NSAIDs (can worsen hemorrhagic sequelae)

## Viral hepatitises (Table 5-2)

### Viral-associated trichodysplasia of immunosuppression

- Occurs in **solid organ transplant patients** or leukemia/lymphoma patients on chemotherapy
- **Polyomavirus** → collections of pink/flesh-colored spiny papules on face (esp. **mid face**), eyebrow/eyelash loss, and thickening of facial skin
- Histology: **eosinophilic cells with trichohyaline granules within hair follicles**
- Decreasing immunosuppressive agents can help, as can topical cidofovir and oral ganciclovir

**Table 5-2.** Cutaneous Manifestations of Hepatitis B and/or C Infection

Small vessel vasculitis (B, C)	<b>Necrolytic acral erythema (C)</b>
<b>Cryoglobulinemic vasculitis (C&gt;B)</b>	Porphyria cutanea tarda (B, C)
Urticarial vasculitis (B, C)	Pruritus (B, C)
<b>Polyarteritis nodosa (B (classic)&gt;C)</b>	<b>Lichen planus</b> – particularly erosive oral disease (C)
Livedo reticularis (C)	<b>Sarcoidosis (with interferon and/or ribavirin therapy; C&gt;B)</b>
Serum sickness-like reaction (B, C)	Erythema multiforme (B, C)
Urticaria (B, C)	Erythema nodosum (B>C)
<b>Gianotti–Crosti syndrome (B&gt;C)</b>	

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

## 5.2 HIV/AIDS DERMATOLOGY

### HIV-associated inflammatory dermatoses

- **Acute exanthem of primary HIV infection**
  - ≤50% of newly infected patients; presents in conjunction with classic **mononucleosis-like syndrome** of primary HIV infection, typically within 6 weeks of transmission
  - Rash may be limited or widespread, is often asymptomatic, and is typically characterized by ill-defined erythematous maculopapules
- **Eosinophilic folliculitis**
  - Characterized by eosinophil-rich inflammatory infiltrate in or around hair follicles
  - **Intensely pruritic**, erythematous, and follicularly based **papules** located on the upper trunk, face, neck, and scalp
- **Aphthous stomatitis**
  - Lesions most often occur on mobile, nonkeratinized oral mucosal surfaces, but esophageal and anogenital aphthae are not uncommon in HIV patients
  - Treatments: topical anesthetics, potent topical steroids, intralesional steroids, systemic corticosteroids, and thalidomide (severe or refractory disease)
- **Erythema elevatum diutinum**
  - In HIV, often associated with β-hemolytic strep infection
  - Dapsone = treatment of choice
  - Oral antibiotics indicated for Streptococcus-associated cases
- **Pruritic papular eruption**
  - Intensely pruritic condition commonly seen in patients with advanced HIV in developing world
  - May represent aberrant immunologic response to insect bites or reactivation of prior bites
  - Patients present with extensive, skin-colored-to-hyperpigmented, excoriated papules
- **HIV photodermatitis**
  - Group of photodistributed rashes with multiple clinical manifestations including lichenoid (most common), eczematous, hyperpigmented, and vitiliginous
  - Exposure to certain photosensitizing medications, particularly trimethoprim-sulfamethoxazole, can increase risk
  - Treatment difficult; strict photoprotection and topical steroids; thalidomide in refractory cases

### HIV-associated infectious dermatoses

- **Oral hairy leukoplakia** (see EBV section)
- **HSV**
  - Can present in the anogenital region as exophytic, **verrucous lesions**, termed herpes vegetans or **hypertrophic HSV**
  - Herpes vegetans is **often acyclovir-resistant** and intralesional cidofovir has been used for refractory cases

- Large, longstanding, ulcerative herpetic lesions refractory to treatment can be seen in patients with profoundly low CD4<sup>+</sup> counts
- **Herpes zoster**
  - HIV testing indicated for patients <50 years old presenting with herpes zoster
  - Atypical presentations, such as disseminated zoster and multidermatomal zoster, are not uncommon
- **HPV**
  - Large, extensive, and/or treatment-resistant HPV-induced lesions, sometimes with malignant transformation, are commonly observed in HIV patients
  - Unusual presentations of HPV infection can be observed (e.g., acquired epidermodysplasia verruciformis-like lesions a/w HPV types 5 and 8)
- **Bacillary angiomatosis**
- **Molluscum contagiosum**
  - Lesions in AIDS patients commonly seen on face and often lack classic dome-shape and central umbilication; may be >1 cm (**giant molluscum**)
  - Treatment: destructive therapies (e.g., curettage, cryotherapy, and trichloroacetic acid)
  - Topical/intravenous cidofovir useful in refractory cases
- **Cytomegalovirus**
  - Can colonize areas of HSV ulceration in patients with CD4<sup>+</sup><50 cells/mm<sup>3</sup>
    - Successful treatment of HSV → clearance of CMV colonization
  - While HSV is typically the driving pathogen in these ulcers, there are reports of ulceration in HIV-infected individuals caused by CMV alone
- **Proximal white subungual onychomycosis**
- **Disseminated mycoses**
  - Disseminated infection caused by *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, or *Penicillium marneffei* should be considered in AIDS patients presenting with **umbilicated, molluscum-like lesions**

### HIV and cutaneous malignancies

- **Basal cell carcinoma, squamous cell carcinoma, and melanoma**
  - HIV patients at ↑risk of developing NMSCs and melanoma (BCC > SCC > melanoma)
  - HIV infection → ↑risk posttreatment recurrence (esp. SCCs)
  - In addition to photo-induced SCCs, also ↑risk of developing HPV-induced intraepithelial neoplasia and SCCs, most commonly of anogenital skin
- **Kaposi sarcoma**
  - Involvement of oral mucosa and genitals more commonly in HIV-associated KS
  - May even be seen in patients with longstanding/well-controlled HIV
  - Treatment options for limited/localized disease: initiation or resumption of antiretrovirals, intralesional chemotherapy (e.g., vinblastine), radiation, cryotherapy, excision, and topical retinoids (e.g., alitretinoin)



**Table 5-3.** HIV-Associated Dermatoses by CD4<sup>+</sup> Count

>500 cells/mm <sup>3</sup>	<500 cells/mm <sup>3</sup>	<200 cells/mm <sup>3</sup>	<50 cells/mm <sup>3</sup>
Acute exanthema of primary HIV infection	Psoriasis	Kaposi sarcoma	Large, nonhealing herpes simplex related ulcerations
Seborrheic dermatitis	Herpes zoster	Eosinophilic folliculitis	Giant molluscum
Oral hairy leukoplakia	HPV	Molluscum contagiosum	Pruritic papular eruption
Vaginal candidiasis	HSV Staphylococcal infections Oropharyngeal candidiasis	Major aphthae (<100) Bacillary angiomatosis Disseminated coccidiomycosis, histoplasmosis; Cryptococcus (<100) Xerosis, eczematous dermatitis, acquired ichthyosis Crusted scabies	HIV photodermatitis

- Treatment for extensive cutaneous disease, or disease involving lymph nodes or viscera: initiation or resumption of antiretrovirals in addition to systemic chemotherapy (doxorubicin most common)

## HIV treatment-associated dermatoses

- Immune reconstitution inflammatory syndrome (IRIS)
  - Pathologic **inflammatory response** to preexisting antigen that develops soon after initiation of antiretroviral therapy in the **setting of decreasing viral load, +/- corresponding increase in CD4+ counts**
  - Cutaneous manifestations of IRIS: development or worsening of infectious entities, neoplastic conditions, and inflammatory dermatoses (summarized in [Tables 5-3 and 5-4](#))
  - Most commonly occurs 2 weeks to 3 months after initiation of antiretroviral therapy
  - Cutaneous IRIS events rarely require discontinuation of antiretroviral therapy – findings typically improve/resolve after several months
- Antiretroviral-associated lipodystrophy
  - Caused by **protease inhibitors**, nucleoside reverse transcriptase inhibitors, and to lesser extent, nonnucleoside reverse transcriptase inhibitors
  - Can manifest as lipoatrophy (loss of fat in face, extremities, and buttocks) or lipohypertrophy (accumulation and redistribution of fat to upper back, neck, or abdomen)
  - Typically seen  $\leq 2$  years of starting therapy
  - Associated with **metabolic abnormalities** (e.g., hyperlipidemia and insulin resistance)
  - **Poly-L-lactic acid** and **calcium hydroxylapatite** approved for treatment of antiretroviral-associated facial lipoatrophy
- Pigmentary alteration
  - **Zidovudine** can cause nail and mucocutaneous hyperpigmentation (longitudinal streaks or diffuse hyperpigmentation of fingernails/toenails)
- Morbilliform exanthems
  - **NRTIs** are common cause of morbilliform exanthems
  - Typically mild and variably symptomatic – pruritus most common complaint
  - In most cases, treatment with inciting agent can be continued – rash will resolve over several weeks

**Table 5-4.** Common Cutaneous IRIS Events

Infectious	Inflammatory	Neoplastic
HSV-1 and HSV-2	Eosinophilic folliculitis	Kaposi sarcoma
VZV (Herpes-zoster)	Acne vulgaris	
HPV	Acne rosacea	
CMV	Seborrheic dermatitis	
Molluscum contagiosum	Foreign-body reactions	
Mycobacteria (leprosy, tuberculosis, and atypical mycobacteria)		
Disseminated fungal (Cryptococcus and histoplasmosis)		
Leishmaniasis		

- Drug-induced hypersensitivity syndrome (DIHS/DRESS)
  - **Abacavir** is the most common antiretroviral to cause DIHS/DRESS (up to 8% patients; can be **fatal**)
  - HLA-B\*5701 linked with abacavir hypersensitivity syndrome – screen patients before initiating therapy
  - Other common causes of DIHS/DRESS in HIV patients: **trimethoprim-sulfamethoxazole** and **dapsone**
- Retinoid-like effects
  - Associated with protease inhibitors, particularly **indinavir**
  - Clinical manifestations: chronic paronychia, **periungual pyogenic granulomas**, alopecia, cheilitis, and xerosis
- Injection-site reactions
  - Reported in most patients treated with enfuvirtide
  - SEs: erythema, ecchymosis, induration, nodules, cysts, and localized sclerosis

## 5.3 BACTERIAL INFECTIONS

### I. Gram-positive skin infections

#### Staphylococcal skin infections

- Impetigo
  - **Most common bacterial infection in children**
  - 35% of population carry *S. aureus* (**anterior nares**>perineum>axilla, toe webs) → ↑risk impetigo

- Non-bullous impetigo (70%): *S. aureus* (>*Streptococcus pyogenes*); **children** > adults
  - Most commonly see erosion + “honey-colored” **crust**; affects **traumatized, abraded, or eczematous skin**; most commonly **face** (perioral/perinasal); self-resolves in 2 weeks
  - Histology: neutrophilic microvesiculopustules, spongiosis, and Gram(+) cocci
- Bullous impetigo (30%): **phage group II (types 55 and 71)** *S. aureus* → produce **exfoliatins A and B** (ETA and ETB) → cleaves **desmoglein 1** → **subcorneal/intragranular acantholysis**
  - Children > adults; presents with (p/w) **flaccid bullae** + erosions w/ **collarette of scale**, minimal surrounding erythema; affects **intact skin**, has more **generalized** distribution
  - Histology: **subcorneal/intragranular acantholysis**, **neutrophils** in blister cavity, Gram(+) cocci
- Treatment:
  - Localized: **topical** Mupirocin, retapamulin, or fusidic acid
  - Widespread: **oral**  $\beta$ -lactamase resistant PCN or first generation CSN or clindamycin
  - Complicated: **IV** ceftriaxone
- **Decolonization**: used for patients w/ recurrent infections; topical mupirocin BID to nares for 7 to 10 days +/- skin decolonization w/ mupirocin ointment or chlorhexidine washes
- **Other high-yield facts**
  - Nonbullous impetigo caused by *S. pyogenes* serotypes 1, 4, 12, 25, and 49 → **poststreptococcal glomerulonephritis** in 5%; risk not altered by antibiotics
  - **No risk of rheumatic fever** from streptococcal impetigo (vs streptococcal pharyngitis)
  - **Bullous impetigo + renal insufficiency** or immunodeficiency → exfoliatin may disseminate → **staph scalded skin syndrome**
  - ETA is chromosomally encoded
  - ETB is plasmid encoded
  - Bullous impetigo and *P. foliaceus* have nearly-identical histology → need DIF and culture
- **Bacterial folliculitis**
  - ***S. aureus* folliculitis**: most common form; most commonly on **face** (beard area typically)
    - Superficial form (Bockhart’s impetigo): small papulopustules on erythematous background
    - Deep form (“**sycosis barbae**”): large red papulopustules +/- plaques with small pustules
  - **Gram(-) folliculitis**: seen in **acne** patients on **long-term ABX**
  - **Pseudomonal folliculitis**: a/w poorly chlorinated **hot tubs/whirlpools**
  - Treatment:
    - Superficial Staph folliculitis: chlorhexidine washes
    - Widespread Staph folliculitis:  $\beta$ -lactamase resistant PCN or first gen. CSN
    - Gram(-) folliculitis: **isotretinoin**
    - Pseudomonal folliculitis: **self-resolves**; ciprofloxacin if severe
    - Decolonization of nares/skin helpful if recurrent
- **Abscesses, furuncles, and carbuncles**
  - All are walled off collections of pus, most commonly from *S. aureus* (often MRSA); may be complicated by surrounding **cellulitis/phlebitis**
  - Abscess: inflamed and fluctuant nodule; arises on **any site**
  - Furuncle: only occurs in a/w hair follicles/on **hair-bearing sites** (“FURuncle = FURry sites”); **head/neck (#1 site)** >intertriginous zones, thighs, other sites of friction
  - Carbuncle: collection of furuncles, often **deeper** w/ **multiple draining sinuses**; most often affects thick skin of **posterior neck, back, and thighs**; systemic symptoms typically present
  - Treatment:
    - Simple abscesses/furuncles: warm compresses or I&D
    - Complicated (sensitive locations, extensive disease, a/w cellulitis/phlebitis, systemic symptoms, and immunosuppressed): **doxycycline**, **TMP/SMX**, and **clindamycin** (depending on local resistance patterns)
    - **Culture necessary since frequently due to MRSA**
    - Decolonization of nares/skin helpful if recurrent
- **MRSA**
  - Most common cause of purulent infections presenting to ED; most commonly p/w **furunculosis** mistaken clinically for “**spider bite**”; may be a/w cellulitis, and necrotic plaques (>necrotizing fasciitis and toxic shock syndrome)
  - Resistance because of ***mecA* gene** (encodes penicillin-binding protein, **PBP2a**) → ↓affinity for  $\beta$ -lactams
  - CA-MRSA (majority) also has Panton-Valentine leukocidin (**PVL**) virulence factor; a/w **increased virulence**, leading to more severe necrosis of skin and other tissues
  - Treatment:
    - Minor infection: **TMP/SMX**, **minocycline/doxycycline**, or **clindamycin** (also covers group A strep)
    - Severe infection: **vancomycin** (best choice); linezolid, daptomycin, and telavancin as second line
- **Staphylococcal scalded skin syndrome (SSSS)**
  - Most commonly **infants/young children** (**low mortality, <5%**) who lack neutralizing antibodies and have ↓renal clearance
  - Also seen in **adults w/ CRF** (**high mortality, >50%**); M > F (2–4 : 1)
  - p/w **febrile prodrome**, widespread **skin tenderness**; skin eruption **begins on face** (**periorificial radial fissuring**) and **intertriginous zones** (**Fig. 5-3**) → generalizes within 48 hours as **wrinkled-appearing** skin w/ **flaccid bullae** and (+)Nikolsky sign → desquamation continues for up to 1 week, then **heals without scarring**
  - Pathogenesis: infection by **phage group II (types 55 and 71)** *S. aureus* at a different/distant site → production of **exfoliatins A & B** (ETA, ETB)→exfoliatins disseminate via



**Figure 5-3.** Staphylococcal scalded skin syndrome. Extensive involvement on the neck with a wrinkled appearance of the erythematous skin in addition to peeling and multiple erosions. (Courtesy, Louis A Fragola, Jr, MD. *Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd edn. Elsevier, 2012.*)

bloodstream → widespread cleavage of Dsg1 → subcorneal/intracorneal acantholysis

- Histology: resembles *P. foliaceus*; lacks inflammatory cells and bacteria in blisters (vs bullous impetigo)
- Cultures from bullae are negative; blood cultures almost always negative in children, but often positive in adults
- Treatment:
  - Mild disease:  $\beta$ -lactamase resistant PCN (dicloxacillin) or first generation CSN (cephalexin)
  - Severe disease: hospitalization + IV ABX
- Other high-yield facts
  - Same exfoliatins as bullous impetigo (ETA/ETB), but hematogenously disseminated
  - Most common primary sites of infection in children = nasopharynx or conjunctivae (vs pneumonia and bacteremia in adults)
- Staphylococcal toxic shock syndrome (S-TSS)
  - Severe multisystem disease with cutaneous and internal involvement (renal > GI, MSK, CNS, hepatic, hematologic, and mucosal)
    - Typically affects young, healthy adults; occult primary site of infection
    - Two forms: “menstrual TSS” (<50% of cases; young women w/ superabsorbent tampons; mortality rate less than 5%) or “nonmenstrual TSS” (>50%; M = F; a/w nasal packing, surgery, skin, or internal infections; mortality rate <20%)
      - ◆ Both forms p/w high fever (>102°F) + rash + systemic symptoms + hypotension (100%)
      - ◆ Mucocutaneous eruption classically starts w/ scarlatiniform eruption (initially on trunk → becomes generalized), redness and edema of palms/soles, “red strawberry tongue,”

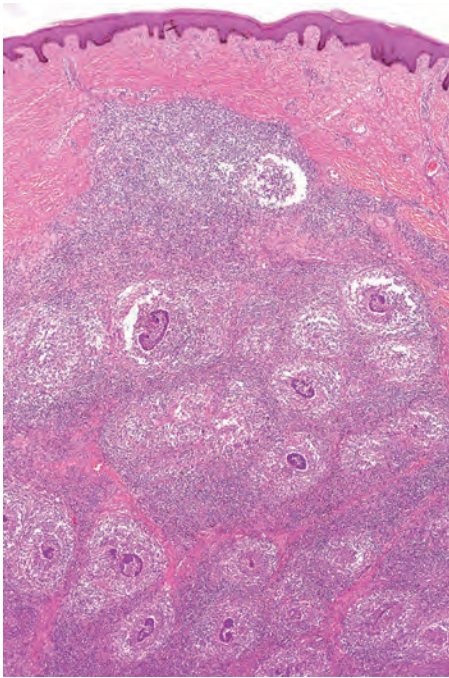
conjunctival hyperemia → palmoplantar desquamation (1 to 3 weeks later), Beau’s lines, onychomadesis; usually negative blood cultures (<15% positive); low mortality (<5% for menstrual TSS and <20% for nonmenstrual TSS)

- Pathogenesis: production of toxic shock syndrome toxin-1 (TSST-1) by certain strains of *S. aureus* → TSST-1 acts as superantigen, binding to V $\beta$  region of TCR and class II MHC on APCs → nonspecific activation of T-cells + cytokine storm ( $\uparrow$ TNF- $\alpha$ , IL-1, IL-6, TLR2, and TLR4)
- Treatment:
  - $\beta$ -lactamase resistant ABX, clindamycin (suppresses toxin production) +/- IVIG; IV fluids for hypotension
- Other high-yield facts
  - vs strep toxic shock syndrome, Staph-TSS has lower mortality (3%–20% vs 30%–60%), less florid primary site infection, more frequent rash, and less frequent blood culture positivity (<15% vs >50%)
- Pyomyositis
  - *S. aureus* infection of skeletal muscle; usually have predisposing factors (immunosuppression, diabetes, trauma, and IVDA); p/w 1 to 2 week febrile prodrome, muscle pain, and a soft tissue mass w/ surrounding woody induration → muscle abscess +/- septicemia
  - Treatment: I&D + IV antibiotics
  - MRI is best diagnostic tool
- Botryomycosis
  - Deep granulomatous and suppurative infection most frequently caused by *S. aureus*
  - May extend to skeletal muscle and bone; affects all ages; a/w  $\downarrow$ T-cell counts and other defects in cellular immunity
  - 70% have skin-limited disease (rarely visceral in severely immunosuppressed patients; lung most common); p/w deep, ulcerative plaques/nodules with multiple draining sinuses that drain yellow granules
  - Histology: large granules w/ basophilic center (nonfilamentous bacteria) and eosinophilic/hyaline periphery (Splendore-Hoeppli phenomenon; comprised of IgG and C3 deposits), granules are surrounded by abscess and granulomatous inflammation (Fig. 5-4); granules are PAS+, Giemsa+, and Gram(+)
  - Treatment:
    - Surgical debridement + antistaphylococcal antibiotics

## Streptococcal skin infections

- Ecthyma
  - Deep variant of impetigo; most common in children; caused by *Streptococcus pyogenes*; p/w few vesicopustules, most commonly on legs → develop into “punched-out” ulcers with purulent base and hemorrhagic crust → slowly self-resolves w/ scarring





**Figure 5-4.** Botryomycosis: there are multiple dermal abscesses surrounding discrete bacterial colonies. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)



**Figure 5-5.** Erysipelas on the malar cheek. (With permission from Habib TP. *Clinical dermatology: a color guide to diagnosis and therapy*, 5th edn. Philadelphia: Elsevier, 2010.)

- Frequently as a result of scratching bug bites
- Histology: well-circumscribed ulcer w/ overlying impetiginized scale crust and dense underlying dermal neutrophilic inflammation
- Labs: wound culture confirmatory, blood culture-negative
- Treatment:  $\beta$ -lactamase resistant PCN (dicloxacillin) or first generation CSN (cephalexin)
- Erysipelas ("St. Anthony's Fire")
  - More superficial variant of cellulitis (upper-mid dermis vs deep dermis/SQ) with sharply defined ("ridge-like") borders, fiery-red color, and pain or burning sensation; prominent lymphatic involvement; most common sites = lower extremity (#1 site) > face (Fig. 5-5)
    - Lymphedema is major risk factor
  - Caused by group A  $\beta$ -hemolytic strep
  - Labs: wound/blood cultures usually negative; best confirmatory tests =  $\uparrow$ DNase B and ASO titers
  - Treatment: penicillin (treatment of choice) for 10 to 14 days; erythromycin if PCN-allergic
- Perianal streptococcal skin infection
  - Classically boys >4 years old; p/w sharply defined red plaques spreading up to 3 cm from anus; a/w pain upon defecation, blood in stool, guttate psoriasis outbreak
  - Labs: skin culture confirmatory
  - Treatment: oral cefuroxime (treatment of choice) or penicillin (slightly less effective)
- Blistering distal dactylitis
  - Initially p/w darkening of skin of distal finger (>toe) volar fat pad  $\rightarrow$  progresses to purulent vesicle/bulla on erythematous background within 1 week; affects children; as a result of picking of nose or local skin trauma; *S. pyogenes* > *S. aureus*
    - Treatment: I&D + 10-day course oral  $\beta$ -lactam
- Scarlet fever
  - Young children (1–10 years old); caused by group A  $\beta$ -hemolytic streptococcus  $\rightarrow$  produces streptococcal pyrogenic toxins A, B, and C (SPE-A, B, and C)
  - Most commonly in setting of streptococcal pharyngitis/tonsillitis; p/w sore throat, high fevers, and systemic symptoms  $\rightarrow$  1 to 2 days later, macular erythema on upper trunk/neck  $\rightarrow$  soon develop classic "sandpaper-like" papular eruption, Pastia's lines (linear petechiae; favors flexural sites), flushed cheeks with circumoral pallor, and "white strawberry tongue" (white background + red papillae)  $\rightarrow$  later "red strawberry tongue," purulent exudate from throat  $\rightarrow$  1 to 2 weeks later, palmoplantar desquamation
    - Labs: positive throat/nasal culture confirmatory; also have elevated DNase B and ASO titers
    - Treatment: PCN (treatment of choice), amoxicillin, or erythromycin (if PCN allergic)
    - Other high-yield facts:
      - Notable complications: acute glomerulonephritis and rheumatic fever
      - Purulent pharyngitis almost always present (helpful clue)
      - 10% of all pts w/strep throat develop scarlet fever; mortality rate has dropped hugely since advent of antibiotics (1% currently vs. 20% mortality in pre-antibiotic era)
- Streptococcal toxic shock syndrome
  - Similar clinical features as Staph-TSS, but affects young/healthy adults, is more severe w/ higher mortality (30%–60%), usually a/w florid skin/soft-tissue infections (often necrotizing fasciitis vs occult infections in Staph-TSS), much less frequent



generalized macular erythematous rash, and far more frequent blood culture positivity (>50%)

- Most common primary source = skin infection from skin barrier breakdown (excoriation, bug bite, and infected surgical site)
- Classically p/w severe localized pain in extremity w/ redness, swelling or necrotizing fasciitis → within 24 to 48 hours, systemic symptoms (hypotension [100%])
- Pathogenesis: group A  $\beta$ -hemolytic strep (M types 1 and 3) produce various toxins:
  - SPE A, B, and C
  - Streptococcal mitogenic toxin Z (SMEZ)
  - Streptolysin O
- Toxins act as superantigens, binding to V $\beta$  region of TCR and class II MHC on APCs → nonspecific activation of T-cells + cytokine storm ( $\uparrow$ TNF- $\alpha$ , IL-1, IL-6, TLR2, and TLR4)
- Treatment: most cases severe, requiring hospitalization + surgical debridement of soft-tissue infection (possibly fasciotomy or amputation) + clindamycin (inhibits toxin production) + PCN +/- IVIG

## Polymicrobial Gram-positive skin infections

- Cellulitis
  - Infection of deep dermis/SQ most commonly affecting adults w/ skin barrier disruption; p/w tender/red/warm, ill-defined plaques w/ fever/chills/lymphangitis
    - In severe cases, may see necrosis, bullae, vesicles
  - Most commonly caused by group A  $\beta$ -hemolytic strep > *S. aureus* (most common cause in children); most common sites: head/neck (children), lower extremities (adults), and IV injection sites on arms (IVDA)
  - Labs: blood cx ~always negative in immunocompetent patients
  - Notable variants:
    - *H. influenzae* (discussed in Gram negative infection section)
    - Cellulitis a/w diabetic ulcers or chronic decubitus wounds: mixed infection w/ Gram(+) cocci and Gram(-) aerobes and anaerobes
  - Treatment:
    - Uncomplicated cases: oral dicloxacillin, cephalexin, or clindamycin for 10 days (must empirically cover for Staph and Strep)
    - Cellulitis a/w diabetic/decubitus ulcers: piperacillin/tazobactam, or ciprofloxacin + metronidazole
    - Severe cases: hospitalize and IV antibiotics
    - MRSA cellulitis: TMP/SMX, minocycline/doxycycline, and clindamycin
  - Other high-yield facts
    - Lymphatic damage from prior cellulitis and lymph node dissection →  $\uparrow$  risk of recurrent cellulitis
    - Presence of abscess or necrotizing cellulitis are clues to MRSA

- Necrotizing fasciitis

- Rapidly progressive, life-threatening (up to 50% mortality) necrotizing infection of skin, SQ, and fascia
- Most common site = extremities (>trunk)
- Caused by group A  $\beta$ -hemolytic strep M types 1 and 3 (#1 cause in children) or polymicrobial (#1 cause in adults; mixture of *Streptococci*, *S. aureus*, *E. coli*, *Clostridium*, and *Bacteroides*)
- Initially p/w severely painful indurated/"woody" plaque ("pain out of proportion to visible skin changes") → over 1 to 2 days and rapidly progresses → color changes from erythematous → dusky purple/gray +/- hemorrhagic bullae/ulceration, crepitus, foul-smelling discharge; patients always severely toxic-appearing (fever, tachycardia, and septic shock) → late in course and skin becomes anesthetic (nerves destroyed)
- Imaging: MRI may demonstrate gas
- Fournier's gangrene: NF of genitalia/perineum/lower abdominal wall
- Meleney's gangrene: polymicrobial NF arising as a postoperative complication
- Treatment: fasciotomy + IV abx (piperacillin/tazobactam + clindamycin + ciprofloxacin)
- Other high-yield facts
  - Risk factors: diabetes, immunosuppression, PVD, CRF, trauma, IVDA, and recent surgery
  - Prognostic factors a/w  $\uparrow$ mortality: older age,  $\uparrow$ time to first debridement,  $\uparrow$ extent of infection, females,  $\uparrow$ lactic acid, and  $\uparrow$ creatinine

## Corynebacterial skin infections

- Erythrasma
  - Caused by *C. minutissimum* (Gram(+) filamentous rod)
  - Affects stratum corneum of moist, intertriginous zones (groin and toe webs (particularly fourth) > axillae, inframammary, umbilicus, and intergluteal)
    - Fluoresces "coral red" w/ Wood lamp (bacterial coproporphyrin III production)
    - Groin: light red-pink slightly scaly patches w/ thin scale
    - Toe webs: chronic, asymptomatic fissuring and maceration
    - Histology: filamentous Gram(+) rods within stratum corneum
  - Treatment:
    - Localized: 20% aluminum chloride, topical clindamycin/erythromycin
    - Widespread/recalcitrant: oral erythromycin and tetracyclines
- Pitted keratolysis
  - Caused by *Kytococcus sedentarius*, which digests keratin in stratum corneum
  - Noninflammatory infection of weight-bearing areas of plantar (>palmar) skin
  - p/w small crateriform pits and foul odor → may coalesce into arciform pits
    - RFs: hyperhidrosis and occlusion

- Histology: sharply demarcated, deep pits in stratum corneum with **Gram(+) bacteria** at base of pits
- Treatment: topical **erythromycin** (or clindamycin, mupirocin, and azole antifungals) +/- 20% aluminum chloride, or botulinum toxin for hyperhidrosis
- **Trichomycosis axillaris**
  - Asymptomatic, **adherent yellow-red concretions** on **axillary hair shafts**; fluoresces with Wood lamp; caused by *Corynebacterium tenuis*
  - Treatment: **shaving** of axillary hair (treatment of choice); may use topical erythromycin/clindamycin

## Clostridium skin infections

- **Clostridial anaerobic cellulitis and myonecrosis**
  - Very rapid, potentially fatal **necrotizing soft tissue infection** with localized gas production ("gas gangrene")
    - Caused by *Clostridium perfringens* (Gram(+), spore-forming rod)
    - Obligate anaerobe (only reproduces in hypoxic tissues)
  - Due to **traumatic inoculation (surgery or crush/penetrating injuries)** of *C. perfringens* into oxygen-poor deep tissues; bacteria produces two pathogenic toxins: **α-toxin** (cleaves lipids) and **perfringolysin** (induces vascular clots and worsens tissue hypoxia) → bacteria proliferates freely in anaerobic environment, producing CO<sub>2</sub> and cleaving lipids → clinically p/w **crepitus**, **foul-smelling brown exudate** ("dirty dishwasher color), w/ variable skin changes
    - RFs: diabetes, PVD
  - Imaging: **X-ray reveals gas** in soft tissues
  - Labs: blood culture usually negative
  - Treatment: immediate **aggressive surgical debridement** (most important) + clindamycin and third gen CSN +/- hyperbaric oxygen

## Filamentous bacteria

- **Actinomycosis**
  - Agent: *Actinomyces israelii*
  - Gram(+), **nonacid fast**, and anaerobic/microaerophilic filamentous bacteria
  - Actinomycetes spp. are part of **normal flora** of mouth, GI/GU tracts → infection arises after **trauma (dental procedures or surgical interventions)**
  - Subacute-chronic granulomatous lesions with **suppurating abscesses + sinus tracts**
  - Forms:
    - Cervicofacial (most common, accounts for 70%): "**lumpy jaw disease**," red-brown nodules with fistulous abscesses draining characteristic **yellow sulfur granules** (= clumps of bacteria); a/w **poor dental hygiene and dental procedures**
    - Pulmonary/thoracic: as a result of aspiration, p/w **pulmonary cavities** at base of lungs
    - GI: as a result of trauma or inflammatory disease, p/w granulomatous lesions in bowel wall
  - Histology: dense granulomatous and suppurative inflammation with "**granules**" with basophilic

center (Gram(+)) branching filaments of *Actinomyces*) and **eosinophilic rim (Splendore-Hoepli phenomenon)**

- Treatment: **Penicillin G** or ampicillin
  - Chronic or deep-seated infections: 2 to 6 weeks of IV abx followed by 3 to 12 months of oral PCN
  - Acute infections: 2 to 3 weeks of oral PCN + I&D of abscesses + surgical excision of sinus tracts
- **Nocardiosis**
  - Agent: *Nocardia brasiliensis* (#1 cause of **actinomycotic mycetoma**), *N. asteroides* (#1 cause of pulmonary/systemic nocardiosis), other *Nocardia* spp.
  - Gram(+), **weakly acid-fast**, filamentous bacteria
  - **Ubiquitous in soil** (explains why foot is most common site of actinomycotic mycetoma!)
  - Four major forms of disease (see Table 5-5), but actinomycotic mycetoma is most testable
  - Histology: intense neutrophilic infiltrate + **sulfur granules** (only seen in actinomycotic mycetoma form); branching filaments are Gram(+), AFB+ (Fite > Ziehl-Neelsen), and GMS+
  - Treatment: **sulfonamides** (treatment of choice) +/- surgical drainage (Box 5-1)

**Table 5-5.** Four Major Clinical Forms of Cutaneous Nocardiosis

Primary	
<b>Actinomycotic mycetoma</b>	Half of all cases of actinomycotic mycetoma are caused by the <i>Nocardia</i> species* <b>Traumatic inoculation</b> causes a painless nodule that enlarges, suppurates, and drains via the sinus tracts Purulent discharge contains sulfur granules The <b>foot</b> is the usual site of involvement May involve underlying muscle and bone
Lymphocutaneous	Occurs days to weeks after trauma Appears as a crusted pustule or abscess resistant to antibiotics Ascending lymphatic streaks, a <b>sporotrichoid</b> pattern of papulonodules, and tender palpable lymph nodes may be seen
Superficial cutaneous	Traumatic implantation of foreign objects (including soil and gravel) into the skin The diagnosis is based on a high index of suspicion, lack of response to routine antibiotic treatment, and laboratory results
Secondary	
Pulmonary/systemic	Subcutaneous abscesses of the <b>chest wall</b> Pustules, nodules, and cutaneous fistulae Almost universally fatal if left untreated Most commonly caused by <i>Nocardia asteroides</i>
*In Mexico and Central and South America, <i>N. brasiliensis</i> is the etiology of 90% of actinomycotic mycetomas, whereas in the United States, most mycetomas are caused by true fungi. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)	

### Box 5-1. Mnemonic

Antibiotics of choice for Nocardia vs Actinomyces = "SNAP"  
Sulfonamides = Nocardia, Actinomyces = Penicillin

## Other Gram-positive infections

- **Anthrax**
  - Agent: *Bacillus anthracis*
  - Gram(+), spore-forming rod
  - Three forms (pulmonary, GI, and cutaneous anthrax)
  - Cutaneous anthrax: **most common (>95%) and least fatal form**
    - Arises via **occupational exposure** (“Woolsorter’s disease”) from direct contact w/ infected animals/carcasses
    - Presents 1 week postexposure with purpuric papulovesicle (“**malignant pustule**”) that drains serosanguinous fluid → vesicle ulcerates to form painless/black/necrotic eschar w/ satellite vesicles and edema
  - Treatment:
    - First line (cutaneous anthrax): **quinolone** or **doxycycline** ×2 weeks (treat for 60 days if suspect bioterrorism or possible inhalation exposure)
  - Other high-yield facts:
    - **Early treatment critical!** (20% mortality if untreated, vs ~0% if treated)
    - Virulence factors:
      - 1) Poly-D-glutamic acid **capsule** (resists phagocytosis)
      - 2) **Lethal toxin** = protective antigen + lethal factor (↑TNF- $\alpha$  and IL-1 $\beta$  → septic shock, death)
      - 3) **Edema toxin** = protective antigen + edema factor (↑cAMP → edema)
- **Erysipeloid**
  - Acute, **self-limited** infection; **occupational** disease of **fisherman** or **poultry/fish handlers**; as a result of traumatic inoculation of *Erysipelothrix rhusiopathiae* (Gram(+)) rod; most commonly p/w localized form: **red-violaceous** nonsuppurative cellulitis +/- hemorrhagic vesicles; classically affects **finger web spaces** w/ **sparing of terminal phalanges**
  - Treatment: **penicillin** (treatment of choice), ciprofloxacin (if PCN allergic)
- **Listeria**
  - Most commonly affects **pregnant women**, elderly, and the immunosuppressed as **GI illness** caused by the ingestion of *Listeria monocytogenes* (motile Gram(+) rod) → fever, bacteremia, and meningitis
  - **Rarely see skin lesions** – mostly occurs in setting of neonatal septicemia (from vertical transmission), which p/w disseminated papules/pustules/vesicles
  - Treatment:
    - First line: **ampicillin**
    - Second line: TMP/SMX

- Treatment: **topical quinolone**, vinegar soaks, or **aminoglycoside** solution ×4 months
- **Pseudomonal pyoderma**
  - Superficial erosive infection w/ **blue-green purulent exudate**, “**moth-eaten**” appearance to skin surface, with “**mousy**” or “**grape-like**” odor; may arise at burn sites, in **mixed toe web infections** (Fig. 5-6), and other chronic wounds
  - Treatment: systemic antipseudomonal antibiotics, topical antiseptics, debridement, and drying agents
- **Otitis externa** (“**swimmer’s ear**”)
  - *P. aeruginosa* infection of external auditory canal; p/w edema, skin maceration, and purulent green exudate; tympanic membrane intact; classically **severe pain upon pinna manipulation**
  - Malignant otitis externa (severe variant): usually only in **diabetics** or **immunosuppressed**; persistent drainage w/ excessive granulation tissue extending to bony portion of ear → may result in osteomyelitis of skull base
  - Treatment: topical antipseudomonal agents
- **Pseudomonal folliculitis** (“**hot tub folliculitis**”)
  - Self-resolving *P. aeruginosa* infection arising from poorly chlorinated **hot tubs/whirlpools**; p/w red, perifollicular papulopustules 1 to 2 days postexposure; commonly affects **areas covered by bathing suit**
  - Spontaneously resolves within 2 weeks
  - Treatment:
    - Immunocompetent: no treatment indicated
    - Widespread, immunosuppressed: oral quinolone
- **Pseudomonas hot-foot syndrome**
  - Self-resolving *P. aeruginosa* infection arising from **wading in pools** w/ high concentrations of *Pseudomonas*; p/w **painful**, red-violaceous plaques/nodules on **weight-bearing areas** of plantar surface
  - Histology: identical to idiopathic palmoplantar hidradenitis
  - Treatment: none required; self-resolves



**Figure 5-6.** Superficial infection of the skin with *Pseudomonas*. Note the maceration, erosions, and moth-eaten appearance of the skin. (Courtesy, Kalman Watsky, MD. Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

## II. Gram-negative skin infections

### Pseudomonas

- **Green nail syndrome**
  - **Green/blue-black** nail discoloration; a/w excessive water exposure, nail trauma; from *P. aeruginosa* pyocyanin pigment production



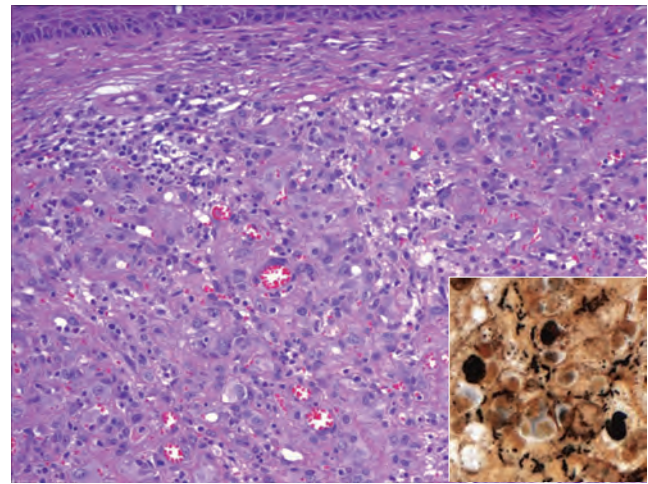
- **Ecthyma Gangrenosum**
  - Cutaneous lesion indicative of *P. aeruginosa* **septicemia**; most commonly occurs in immunosuppressed patients w/ **severe neutropenia** (often BMT patients); p/w a small number of **purpuric macules** → progresses to hemorrhagic bullae → bullae rupture → **ulcer w/ necrotic black eschar** and tender, red skin surrounding eschar; most common sites = **anogenital region and extremities**
  - Histology: sharply demarcated epidermal necrosis w/ hemorrhagic crust, and underlying dermal infarction w/ septic vasculitis (**Gram(-) rods in vessel walls**)
  - Labs: blood/wound cultures positive
  - Treatment: **IV aminoglycoside + antipseudomonal PCN**
  - Other high-yield facts
    - Prognostic factors a/w poor outcomes: ↑# lesions, delay in diagnosis, and prolonged neutropenia

## Bartonella

- Small, facultative **intracellular** Gram(-) bacilli
- Three species cause human disease (Table 5-6):
  - *B. henselae* (cat scratch disease, bacillary angiomatosis, and peliosis hepatitis)
  - *B. quintana* (trench fever, and bacillary angiomatosis)
  - *B. bacilliformis* (Carrión's disease/Oroya fever/verruca peruana)
- Both *B. henselae* and *B. quintana* may cause: bacillary angiomatosis, chronic afebrile bacteremia, and endocarditis
- **Bacillary angiomatosis** mostly occurs in **HIV + patients w/ CD4 count <200**; only 20% recall cat bite/scratch (vs 90% w/ cat scratch disease); vascular proliferation caused by bacterial angiogenic factor
  - Can involve lymph nodes, bone, and viscera
  - Lesions are dome-shaped, vascular papulonodules
  - More developed lesions can have a friable eroded appearance, resembling pyogenic granulomas
- Death in Oroya fever usually secondary to *Salmonella enterica* superinfection; **chloramphenicol** is treatment of choice
- Histopathology (verruca peruana and bacillary angiomatosis): resembles pyogenic granuloma (lobular capillary proliferation), but has **dense neutrophilic infiltrate**, and extra- and intracellular **organisms (within endothelial cells)** seen w/ **Warthin-Starry stain** (Fig. 5-7)
- Labs: **PCR assay** (most rapid and sensitive), *B. henselae* **serologies** (sensitive and specific; cannot be used for *B. quintana*); ELISA; culture on **chocolate agar** (takes up to 40 days)

## Rickettsia

- Small, obligate intracellular Gram(-) organisms
- Transmitted by **arthropod host/vector** (ticks, fleas, lice, and mites)
- Target = **endothelial cells**
- Transmitted from arthropod (tick, flea, mite, and louse) via saliva or feces → bacteria enter dermis via bite or scratching → bacteria **attach to endothelial cells** →



**Figure 5-7.** Bacillary angiomatosis. Histologically, a dermal proliferation of vessels with plump endothelial cells is evident. Scattered neutrophils are also present in the accompanying infiltrate. Bacilli (in this case, *Bartonella henselae*) are identified with the Warthin-Starry stain. (Courtesy, James Patterson, MD. Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

spread hematogenously and destroy infected vessels via **reactive oxygen species** formation → ↑**vascular permeability** → vascular skin findings (petechiae, purpura, and vasculitis = “**spotted fever**”) and life-threatening end organ damage (**meningoencephalitis** and **pulmonary edema/pneumonitis** most important causes of mortality), **thrombocytopenia**, hypovolemia, and hypotension

- **Three groups (Table 5-7):**
  - **Spotted fever group** (rash in 85%–100%): *R. rickettsii*, *R. conorii*, *R. akari*, *R. africae*, *R. japonica*, and *R. australis*
  - **Typhus group** (rash in 50%–80%): *R. typhi* and *R. prowazekii*
  - **Scrub typhus** (rash in 50%): *R. tsutsugamushi*
- **Eschar at inoculation site** is constant and important feature seen in majority of spotted fever group, and scrub typhus
  - **No eschar** in RMSF and typhus group
- Variable prognosis:
  - Severe: **RMSF (most severe, 25% mortality if untreated, and 4% if treated) > epidemic typhus** (15% mortality if untreated and 3% if treated)
  - Intermediate: Mediterranean spotted fever (3–5% mortality)
  - Benign: **endemic typhus** (≤1% mortality) and **Rickettsialpox** (0% mortality)

## Other Gram-negative skin infections

- *Neisseria meningitidis*
  - **Gram(-) diplococcus** (strains A, B, C, Y, and W-135)
  - Most commonly affects children/young adults living in close quarters (**military recruits** and college students); M > F (4 : 1); humans are only reservoir; 10% to 15% **population are asymptomatic carriers** (in nasopharynx); disease transmitted via **respiratory secretions**



Table 5-6. Major Human Diseases Caused by *Bartonella* Species and Their Treatment

Species	Disease	Vector	Reservoir/ host	Epidemiology	Clinical presentation	First Line	Second Line	Notes
<i>B. bacilliformis</i>	<b>Bartonellosis</b> (Carrion's disease, Oroya fever, and verruga peruana)	Phlebotomine sand fly ( <i>Lutzomyia verrucarum</i> )	Human	Andean mountain valley regions of Peru, Ecuador, and Southwestern Columbia (altitudes of 2500–8000 feet) More common in immunologically naive tourists and transient workers Milder in children	Oroya fever (acute phase)	<b>Chloramphenicol*</b> plus $\beta$ -lactam antibiotic Quinolone (norfloxacin and ciprofloxacin) (>6 years of age and not pregnant)	Trimethoprim-sulfamethoxazole Macrolide Doxycycline	Successful treatment does not eliminate risk for developing verruga peruana Adjunctive treatment needed with chloramphenicol, as treatment failures have been seen with monotherapy Death occurs in ~40% of untreated individuals Only 5% of patients recall an acute febrile illness Disappearance of skin lesions within 1 month with treatment
<i>B. henselae</i>	<b>Cat scratch disease</b>	Cat flea ( <i>Ctenocephalides felis</i> )	Cat	Primarily seen in young people (<18 years) in the fall and winter Immunocompetent > immunocompromised	Mild to moderate, uncomplicated  Severe, complicated	Supportive care (analgesics) only Needle aspiration of suppurative lymph nodes Doxycycline plus rifampin	Azithromycin Doxycycline plus rifampin	Azithromycin shown to decrease lymph node volume, but not effective in preventing dissemination or complications Severe disease includes retinitis, encephalopathy, and visceral spread Jarisch-Herxheimer-like reaction may occur Treatment failures seen with quinolones, trimethoprim-sulfamethoxazole, and narrow-spectrum cephalosporins Use of IV antibiotics recommended for GI intolerance or poor absorption states
	<b>Bacillary angiomatosis</b> <i>Bacillary peliosis hepatis</i> Bacteremia (chronic afebrile) Endocarditis			<b>Immunocompromised</b> (e.g., common in HIV) Immunocompromised  Immunocompetent or immunocompromised Late complication of chronic bacteremia	Mild, uncomplicated bacillary angiomatosis  Severe, complicated bacillary angiomatosis	Erythromycin  Erythromycin Doxycycline plus rifampin	Doxycycline Azithromycin Clarithromycin	
<i>B. quintana</i>	<b>Trench fever</b> "Five day fever" "Urban trench fever" "Quintan fever"	<b>Human body louse</b> ( <i>Pediculus humanus</i> )	Human	First reported in World War I troops, now associated with <b>homelessness and poor hygiene</b> ("urban trench fever") Immunocompromised (e.g., common in HIV) Immunocompetent or immunocompromised Late complication of chronic bacteremia		Doxycycline plus aminoglycoside		Doxycycline plus rifampin recommended for CNS disease, because of better CNS penetration
	<b>Bacillary angiomatosis</b> Bacteremia (chronic afebrile) Endocarditis							

Fever and splenomegaly caused by bacteremia with *Bartonella rochalimae* (a recently recognized species) has also been described.

\*Gray baby syndrome can develop in premature neonates who receive chloramphenicol.

(From Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier: 2012)

Table 5-7. Rickettsial Diseases

Disease (bacterium)	Vector	Clinical Features	Rx	Other High-Yield Facts
<b>Spotted fever group:</b> "spotted fever" = high fevers (>102°F) + erythematous-petechial skin eruption (85%–100%) + constitutional symptoms				
Rocky Mountain Spotted Fever ( <i>Rickettsia rickettsii</i> )	<b>Dermacentor variabilis</b> (#1 vector, Eastern 2/3rd and Pacific Coast of the United States) <b>D. andersoni</b> (#2 vector, Rocky Mountain states) <i>Rhipicephalus sanguineus</i> (Southwestern United States)	7–14 days post-tick bite, develop fever, headache, myalgias, and GI symptoms → <b>90% develop rash</b> 3–5 days later with faint red <b>macules</b> on acral sites ( <b>wrists and ankles</b> are most common initial sites) → subsequent <b>centripetal spread</b> to trunk; <b>spares face</b> → over time, lesions become papular and <b>petechial/purpuric</b> as a result of edema and RBC extravasation from vessel destruction; <b>mortality rate = 25%</b> if untreated (vs <4% if treated early)	<b>Doxycycline</b> is treatment of choice in ALL patients, <b>even children!</b> Only exception: <b>chloramphenicol</b> is treatment of choice for <b>pregnant patients</b> (→ risk of "gray baby syndrome")	RMSF is the <b>most severe</b> Rickettsial infection 40% of patients do not recall tick bite! <b>Lacks eschar!</b>
Mediterranean spotted fever/"Boutonneuse fever" ( <i>Rickettsia conorii</i> )	<b>Rhipicephalus sanguineus</b> (brown dog tick)	p/w necrotic papule at site of tick bite (" <b>Tache noir</b> ") → maculopapular eruption favoring <b>legs</b>	First line: <b>doxycycline</b> Mild disease in children: azithromycin, clarithromycin	
Rickettsialpox ( <i>Rickettsia akari</i> )	<b>Liponyssoides sanguineus</b> (house mouse mite)	Within 48 hours of bite p/w <b>papulovesicle</b> at bite site → progresses to <b>eschar</b> (>90%) → fever and systemic symptoms w/ <b>widespread cutaneous eruption (face, trunk, and extremities)</b> of red macules and papulovesicles w/ <b>hemorrhagic crusts</b> +/- oropharyngeal enanthem	<b>None required; self-resolves</b> within 3 weeks May hasten resolution w/ doxycycline	The only spotted fever to be caused by a <b>mite</b> Most common in <b>urban areas</b> of Northeastern United States Well-Felix test does <b>not</b> identify Rickettsialpox
<b>Typhus group:</b> similar to spotted fever group in most regards; p/w erythematous macules starting around <b>axillae</b> ; rash in only <b>50%–80%</b> (vs 85%–100% in spotted fever group)				
Endemic/murine Typhus ( <i>Rickettsia typhi</i> )	<b>Xenopsylla cheopis</b> (Oriental rat flea)	p/w fever + similar systemic symptoms as spotted fever group + erythematous macules and papules initially on <b>axillae</b>	<b>Doxycycline</b>	<b>Xenopsylla cheopis</b> is also the vector for bubonic plague
Cat flea typhus ( <i>Rickettsia felis</i> )	<b>Ctenocephalides felis</b> (cat flea)	Clinically identical to endemic (murine) typhus	<b>Doxycycline</b>	
Epidemic Typhus ( <i>Rickettsia prowazekii</i> )	<b>Pediculus humanus var. corporis</b> (human body louse)	Epidemic typhus: a/w crowded living conditions Brill-Zinsser disease: recurrence of latent infection (occurs decades later) Flying squirrel typhus: caused by contact w/ <b>flying squirrels</b> and their fleas/lce	<b>Doxycycline</b>	
<b>Scrub typhus:</b> solitary member comprising the third group of Rickettsial infection; rash in only 50%				
Scrub typhus ( <i>Orientia tsutsugamushi</i> )	<b>Larval trombiculid mites</b> ("chiggers")	<b>Eschar</b> forms at bite site (60%–90%) → fever, lymphadenopathy, and macular rash (50%) starting <b>initially in axilla</b> → <b>subsequent centrifugal spread</b> ; variable prognosis	First line: <b>doxycycline</b> Pregnant women: azithromycin	Most common in <b>Asia</b> ; particularly areas w/ dense <b>scrub</b> vegetation
<b>Rickettsia-like bacteria</b>				
Human Monocytic Ehrlichiosis ( <i>Ehrlichia chaffeensis</i> )	<b>Amblyomma americanum</b> (lone star tick)	Most common in Southern United States; p/w fever, myalgias, thrombocytopenia, <b>leukopenia</b> , and <b>maculopapular or petechial</b> rash (30%–40%) most commonly on <b>trunk, extremities</b> ; mortality rate = 3%	<b>Doxycycline</b>	Obligate intracellular organism targets and kills <b>monocytes/macrophages</b> Reservoir = <b>white tailed deer</b> <b>No eschar</b> seen
Human Granulocytic Anaplasmosis ( <i>Anaplasma phagocytophilum</i> )	<b>Ixodes scapularis</b> and <b>Ixodes pacificus</b> (same as Lyme and Babesiosis)	Found in same geographic distribution as Lyme disease; similar clinical presentation as HME, but <b>↓fatality rate, ↓skin findings</b> , and ↑peripheral neuropathy	<b>Doxycycline</b>	Obligate intracellular organism targets and kills <b>neutrophils</b> <b>Coinfection</b> w/ Lyme and Babesiosis is common
Q Fever ( <i>Coxiella burnetii</i> )	Usually transmitted via aerosols from infected <b>sheep and cattle</b>	<b>Rare skin findings</b>	<b>Doxycycline</b>	



**Figure 5-8.** Stellate purpura with a central gunmetal-gray hue suggestive of meningococemia. (From *Annals of Emergency Medicine* 2009-08-01; 54:2:155–180 Elsevier, 2009.)

- **Acute meningococemia:** 1 to 10 days postexposure, p/w fever, chills, headache, **petechial rash** (30%–50%), **retiform purpura** w/ classic “gunmetal gray” color (Fig. 5-8), or **hemorrhagic bullae** on legs and trunk; may progress to **septic shock** with DIC (purpura fulminans)
  - Histology: LCV w/ **vascular thrombosis** and **Gram(-) rods** in 70% biopsies
  - Labs: PCR assay most sensitive/specific (>blood/tissue/CSF cultures or latex agglutination studies)
  - Prognosis: **10% to 15% mortality**; up to 15% who survive have **hearing loss** or CNS sequelae
- **Chronic meningococemia:** less common; p/w recurrent fevers, arthralgias, and macular/papular eruption; condition self-resolves, only to recur days to weeks later
- Treatment: early treatment is critical!
  - First line: high-dose IV **penicillin** (treatment of choice)
  - Second line: quinolones or chloramphenicol (if PCN-allergic); third generation CSN (resistant disease)
  - **Prophylactically treat all close contacts** w/ ciprofloxacin, rifampin, azithromycin
- Other high-yield facts
  - Risk factors: **asplenic patient** or **terminal complement deficiency** (C5–C9)
  - **Main virulence factor = polysaccharide capsule**
  - **Endotoxin** → septic shock and **purpura fulminans**
  - In the United States, types B, C, and Y are most common causes of acute meningococemia
  - Quadrivalent vaccine protects against types A/C/Y/W-135
- **Brucellosis** (Malta fever, “undulant fever”)
  - Caused by Gram(-) coccobacillus, *Brucella* spp.
  - Endemic in Middle East (consuming **unpasteurized goat milk/cheese**)
  - In the United States, occupational disease (**farmers, butchers, and veterinarians**) from **direct contact or inhalation**
  - p/w **undulating fevers**, arthralgias, lymphadenopathy, hepatosplenomegaly, and **rare (<10%) skin findings** (disseminated violaceous papules, EN)
  - Treatment: multidrug regimens of **doxycycline** + other antibiotics (streptomycin, rifampin, TMP/SMX, quinolones, and aminoglycosides)
- **Glanders**
  - Gram(-) bacillus, *Burkholderia mallei*
  - Caused by contact w/ **infected horses** or donkeys
  - Four forms:
    - **Localized**—hemorrhagic, ulcerative papulopustule at inoculation site
    - **Chronic**—multiple soft tissue nodules (“farcy buds”) on skin overlying lymphatics
    - **Septicemic form**—mortality rate >95% without treatment and 50% w/ treatment
    - **Pulmonary form**—mortality similar to septicemic form
  - Treatment:
    - Localized disease: 60- to 150-day course of amoxicillin/clavulanate, doxycycline, or TMP/SMX
    - Septicemic: IV carbapenems + ciprofloxacin or doxycycline
- **Melioidosis**
  - Gram(-) bacillus *Burkholderia pseudomallei*
  - Caused by direct contact w/ contaminated **water or soil**
  - RFs: diabetes, alcoholism, immunosuppression, and IVDA
  - Clinical presentation and mortality rates ~same as glanders
  - Treatment: same as glanders
- **Malakoplakia (malacoplakia)**
  - Chronic granulomatous infection as a result of the inability of macrophages to kill phagocytosed *E. coli*
  - Most commonly affects **immunosuppressed** (BMT > HIV/AIDS)
  - Most commonly affects **GU tract**; may affect **skin of perianal/genital** region (ulcerated abscesses and soft polypoid lesions)
  - Histology: dense granulomatous infiltrate comprised of **von Hanseman cells** (large macrophages w/ eosinophilic cytoplasm) containing **Michaelis-Gutmann bodies** (round, laminated, calcified basophilic intracytoplasmic inclusions; comprised of incompletely killed bacteria within calcified phagolysosomes; stain w/ **von Kossa**, PAS, Perls, Giemsa)
  - Treatment:
    - Localized: **surgical excision**
    - Nonsurgical candidates: difficult to treat; may try long courses of ciprofloxacin, TMP/SMX, or clofazimine
- **Tularemia (rabbit fever and deer fly fever)**
  - Gram(-) coccobacillus, *Francisella tularensis*
  - Mode of transmission = contact w/ **rabbit carcasses (classic!)**, deer flies, and ticks; increased risk in **hunters** and animal handlers

- Most common presentation is **ulceroglandular** = 80% (>pneumonic>glandular, typhoidal>oropharyngeal >oculoglandular), which p/w **necrotic, punched-out ulcer** at inoculation site w/ **suppurative lymphadenopathy** (Box 5-2)
- Treatment: **streptomycin** (treatment of choice)
- *H. influenzae* cellulitis
  - Gram(-) coccobacillus
  - Classically affects **infants**, p/w deep **red-violaceous/blue facial cellulitis** (most commonly **periorbital** or **buccal**) following a URI-like illness
  - Usually **positive blood cultures**
  - Treatment: third generation CSN
  - Incidence has decreased since development of **Hib vaccine**
- **Rhinoscleroma**
  - Chronic granulomatous infection of **nose** and upper respiratory tract
  - Affects adults, mainly in **tropical** locations
  - Transmitted by **inhalation** of *Klebsiella rhinoscleromatis*
  - a/w cellular immune defects: inability of macrophages to kill phagocytosed bacteria → **Mikulicz cells** (large, vacuolated histiocytes containing bacteria)
  - Three clinical phases:
    - **Catarrhal phase** (rhinitis, obstruction from soft tissue edema)
    - **Granulomatous/infiltrative phase** (granulomatous nodules in nose/URT, epistaxis, **dysphonia**, **anesthesia of soft palate**, and **Hebra nose**)
    - **Sclerotic phase** (extensive scarring requires tracheotomy and nasal reconstruction)
  - Histology: dense pan-dermal infiltrate of **Mikulicz cells** containing bacteria (seen w/ **Warthin-Starry**, **Giemsa**) and **Russell bodies**
  - Treatment: **tetracycline** (treatment of choice) for 6 months along with surgical correction of airway; ciprofloxacin is second line
- **Salmonellosis** (typhoid fever)
  - Enteric infection caused by *Salmonella typhi*
  - Spread by direct contact w/ infected individuals or carriers
  - p/w fever, nausea/vomiting, diarrhea, headache, and characteristic **“rose spots”** of skin (2- to 8-mm pink, grouped papules on **trunk**); bacteria can be cultured from rose spots
  - Treatment: **quinolones** (treatment of choice); use third gen CSN in children
- **Rat-bite fever** (“Haverhill fever”)
  - *Streptobacillus moniliformis*
  - As a result of a **rat bite** (“rat bite fever”), or occasionally, ingestion of contaminated food (“Haverhill fever”); **↑incidence in urban areas w/ high rat concentration**
- Classic triad (paroxysmal fever, migratory polyarthritis, and acral rash)
  - p/w redness, edema, and ulceration at bite site → paroxysmal fever w/ systemic symptoms → 2 to 4 days later, migratory polyarthritis + acral eruption (**palms and soles** most common) of petechial red macules/papules, vesicles, or pustules
  - Up to **15% mortality**
- Treatment: **penicillin** (treatment of choice) for 1 week (6 weeks if septicemic)
- **Plague**
  - Caused by *Yersinia pestis*, a Gram(-) **bipolar bacillus**
    - Characteristic **“safety pin” appearance** of bacteria on gram or Giemsa stain
  - **Reservoir = rodents**; usually transmitted to humans by **flea bites** (>rodent contact, inhalation)
  - Forms:
    - **Bubonic (most common)**: pustule or ulcer at inoculation site (10%) + **painful, suppurative regional lymphadenopathy** = “**buboes**” (groin, axillae most common); 25% to 50% mortality rate if untreated
    - **Septicemic**: vesiculopustular eruption w/ petechiae, purpura; hemorrhagic and necrotic lesions in nasopharyngeal and GI tracts; 100% mortality if untreated
    - **Pneumonic**: acute pneumonitis; 100% mortality if untreated
  - Treatment:
    - First line: **aminoglycosides** (streptomycin and gentamicin)
    - Plague meningoencephalitis: chloramphenicol (high penetration of blood-brain barrier)
    - Postexposure prophylaxis: doxycycline or ciprofloxacin ×7 days (highly effective)
- *Vibrio vulnificus*
  - Most commonly affects **men >40 years old** who have predisposing factors: **liver disease** (hemochromatosis, cirrhosis, or alcoholism), **diabetes** (peripheral neuropathy/vasculopathy predisposes to wound infections), GI disease, immunosuppression, and ESRD
  - Reservoir = **shellfish**
  - Two modes of infection:
    - **Cutaneous exposure to contaminated seawater/shellfish**: affects shellfish handlers; trauma → primary skin infection, or superinfection of preexisting wound → may progress to **necrotizing fasciitis, myositis, or septicemia**
    - **Consumption of raw/undercooked shellfish**: most commonly from **raw oysters**; septicemia, abdominal cramps, and hypotension; 75% have skin findings – red-purple macules/vesicles → progress to **hemorrhagic bullae and necrotic plaques**
  - Treatment: **doxycycline** + third gen CSN
- **Bite-induced infections**
  - **Dog bites are most common** (>cats >humans); human bites are most likely to get infected

**Box 5-2. Mnemonic****Differential Diagnosis of Ulceroglandular Diseases**

“My Aunt’s Temperamental Tall Rats Plague Glands”

Melioidosis, Anthrax, Tularemia, TB chancre, Rat-bite fever, Plague, Glanders



- Dog bite: *Pasteurella multocida*, *Pasteurella canis*, or *Capnocytophaga canimorsus* (potentially fatal in asplenic or immunosuppressed patients)
- Cat bite: *Pasteurella multocida* > *Streptococcal* spp.
- Human bite: *Eikenella corrodens* (a/w chronic infections), *S. aureus* (a/w severe infections), *Peptostreptococcus*, *Enterococcus*, and *Bacteroides*
- Treatment:
  - Amoxicillin/clavulanate (treatment of choice)
  - Also important to irrigate wound and give tetanus vaccine

### III. Nonvenereal spirochete infections

#### Borrelia

- Lyme disease
  - Agent: *Borrelia burgdorferi* (#1 in the United States); *B. garinii* and *B. afzelii* (#1 in Europe)
  - Reservoir: white-tailed deer and white-footed mouse
  - Vector: *Ixodes* spp. (hard body) ticks; specific type varies by geographic region:
    - *I. scapularis* (*I. dammini*) → #1 cause in the United States (prevalent in Eastern United States and Great Lakes region)
    - *I. pacificus* → western United States
    - *I. ricinus* → Europe
  - Pathogenesis: *Ixodes* tick feeds on infected animal reservoir → spirochetes stored in tick's salivary glands → tick bites human and releases *Borrelia* spirochetes into dermis → erythema migrans develops at bite site 1 to 2 weeks later → if untreated, hematogenous dissemination + systemic symptoms
  - Three clinical stages of Lyme disease:
    - Early localized:
      - ◆ Erythema migrans (90%): initial cutaneous manifestation; develops 7 to 14 days posttick attachment; p/w expanding annular plaque w/ central clearing ("bull's eye" appearance) → reaches >5 cm diameter; favors trunk (#1 site in children), legs (#1 site in adults), and intertriginous areas; lesion self-resolves in 4 weeks if untreated
      - ◆ Disseminated erythema migrans lesions (25%–50%): multiple smaller annular lesions; arise days to weeks after primary erythema migrans lesion
      - ◆ Other: nonspecific flu-like symptoms and regional lymphadenopathy
    - Early disseminated: as a result of hematogenous spread of spirochetes; arises if initial phase untreated
      - ◆ Borrelial lymphocytoma (1%, Europe only): strongly a/w *B. afzelii* and *B. garinii*; p/w firm, plum-colored tender nodule/plaque on earlobes (children), or nipple/areola (adults)
      - ◆ Arthritis (60%): mono/oligo-articular (knee = most common site); arises weeks to months after initial infection
- ◆ Neurologic abnormalities (10%): most commonly Bell's palsy
- ◆ Cardiac complications (5%): A-V block, myopericarditis
- Chronic:
  - ◆ Acrodermatitis chronica atrophicans (10%, Europe only): strongly a/w *B. afzelii* and *B. garinii*; occurs months to years after initial infection; two clinical phases: erythematous plaques with "doughy"/swollen skin on distal extremities (early phase; easily treated/reversible) → progresses to atrophic "cigarette-paper" skin w/ telangiectasias (chronic phase; recalcitrant to treatment) and subcutaneous fibrous nodules overlying joints
  - ◆ Other: encephalopathy, neuropathy, and chronic arthritis
- Diagnosis:
  - Recognition of erythema migrans rash = most sensitive way to confirm Lyme!
  - Serologic evidence of Lyme infection is often lacking early (only 41% positive at 1 to 2 weeks, and 88% positive when checked >2 weeks into infection) → cannot rule out Lyme via negative serologies early in disease course!
  - Tissue PCR/culture: specific, but not sensitive
  - Treatment discussed in Table 5-8
- Other high-yield facts:
  - Peak incidence in summer (80% of cases in the United States arise between June and August)
  - Tick must be attached for >24 hours to transmit Lyme → ↑↑↑risk if >48 hours of attachment
  - Frequent coinfection with Lyme + Babesiosis + HGA (human granulocytic anaplasmosis) → doxycycline covers all three agents
  - European Lyme disease has: larger EM lesions that persist longer, ↓arthritis, and ↑↑neurologic sequelae
- Other Borrelial infections (see Table 5-8)

#### Nonvenereal (endemic) treponematoses

- Yaws, Pinta and endemic syphilis (Bejel) are all caused by *T. pallidum* subspecies that are morphologically and antigenically identical to the organism responsible for venereal syphilis
- All three diseases have primary, secondary, and tertiary stages (Table 5-9)
- Route of transmission: skin, mucous membrane, or fomite contact
- All except Pinta most commonly affect children
- All except Bejel most commonly begin on legs
- Serologic assays used for venereal syphilis are also positive in these diseases, but cannot differentiate between them
  - Treponemal tests (FTA-ABS, MHA-TP, and TPHA): specific for treponemal infections, may remain positive for life
  - Nontreponemal tests (RPR and VDRL): less specific, but useful for identifying current or recent infections, or monitoring response (four-fold decrease =

**Table 5-8.** *Borrelia* Infections

Disease	Agent	Vector	Clinical Features	Prescription
Lyme Disease	<i>B. burgdorferi</i>	<i>Ixodes dammini</i> (Northeast United States and Great Lakes area) <i>Ixodes pacificus</i> (Western United States) <i>Ixodes ricinus</i> (Europe)	As previously discussed in text	First line: <b>doxycycline</b> In pregnancy or children <8 years old → <b>amoxicillin</b> is treatment of choice
Borrelial lymphocytoma	<i>B. afzelii</i> > <i>B. garinii</i>	<i>Ixodes ricinus</i> (Europe)	As previously discussed in text	Doxycycline
Acrodermatitis chronica atrophicans	<i>B. afzelii</i> > <i>B. garinii</i>	<i>Ixodes ricinus</i> (Europe)	As previously discussed in text	Doxycycline
Louse-Borne Relapsing Fever (Africa)	<i>B. recurrentis</i>	<i>Pediculus humanus</i> var. <i>corporis</i> (human body louse)	<b>3–4 relapses of paroxysmal fevers</b> w/nonspecific flu-like symptoms and nonspecific macular or petechial eruption; <b>more severe</b> than tick form	Doxycycline
Tick-Borne Relapsing Fever (Western United States)	<i>B. duttonii</i> <i>B. hermsii</i>	<i>Ornithodoros</i> (soft-bodied ticks)	Like Louse-borne relapsing fever, but only <b>1–2 relapses</b> and less severe	Doxycycline

**Table 5-9.** Nonvenereal Treponematoses

Disease (bacterium)	Most Common Age and Geographic Location	Clinicopathologic Features	Other High-Yield Facts
Yaws ( <i>T. pallidum pertenue</i> )	<u>Age</u> : children <15 years old <u>Location</u> : warm, humid, and tropical climates (Africa, Asia, Central and South America, and Pacific Islands)	<u>1° stage</u> : legs most commonly affected; p/w indurated, red, painless papule that enlarges to 1–5 cm, then ulcerates ("Mother Yaw"); occurs at site of inoculation; may have hypomelanotic macules on dorsal wrists/hands <u>2° stage</u> : multiple smaller widespread "daughter Yaws" <u>3° stage</u> : <b>necrotic and ulcerative abscesses</b> that heal with severe/deforming scars + bony damage	3° stage only occurs in 10% Mnemonic: " <b>Yaws = Jaws</b> " (big, destructive "bites" are taken out of affected skin and bone)
Pinta ( <i>T. pallidum carateum</i> )	<u>Age</u> : <b>all ages</b> equally affected <u>Location</u> : Western hemisphere only (Central and South America)	Skin-only disease <u>1° stage</u> : legs most commonly affected; p/w papules surrounded by red halo; enlarges over months up to 12 cm <u>2° stage</u> : smaller scaly papules and psoriasiform plaques erupt ("pintids") and change in color from <b>red → blue → brown → gray/black</b> <u>3° stage</u> : symmetric <b>vittiligo-like lesions</b> over bony prominences w/atrophic epidermis. Histology shows lichenoid interface + complete loss of melanocytes + epidermal atrophy	Mnemonic: "Pinta <b>only</b> paints the skin different colors" Mnemonic: "Pinta is a Spanish word → limited to <b>Spanish America</b> "
Endemic Syphilis/"Bejel" ( <i>T. pallidum endemicum</i> )	<u>Age</u> : children <15 years old <u>Location</u> : dry, warm climates (North Africa and Southeast Asia)	<u>1° stage</u> : rarely noticed; p/w inconspicuous papule or ulcer in <b>mouth or on nipples of breastfeeding women</b> ; may have hypomelanotic macules on extremities, genitalia, areolae, and trunk <u>2° stage</u> : <b>mucous membrane lesions</b> (mucosal patches, condyloma lata, and angular stomatitis) + generalized lymphadenopathy +/- skin lesions <u>3° stage</u> : Gumma formation of mucous membranes, skin, and bones	Mnemonic: "similar to venereal syphilis, but <b>mucosal disease predominates</b> over skin" or "ENDemic syphilis attacks ENside surfaces"

successful treatment; **four-fold increase** = reinfection/relapse)

- Histology for all three resembles venereal syphilis
- Treatment: **Benzathine PCN** (treatment of choice for all)

## IV. Sexually transmitted bacterial infections

### Syphilis

- Agent: *Treponema pallidum* (Gram(-) spirochete)
- Congenital Syphilis

- **Early congenital (<2 years old)**: snuffles, dactylitis, Parrot's pseudoparalysis, epiphysitis, and hepatitis
- **Late congenital (>2 years old)**: keratitis, mulberry molars, Hutchinson's teeth (notched/peg-shaped incisors), rhagades (linear scars at angles of mouth) saddle nose, Higoumenakis syndrome, Clutton's joints, optic atrophy, corneal opacities, and eighth nerve deafness
- Primary (10- to 90-day incubation (avg = 3 weeks) till chancre)
  - **Chancre** (painless, well-defined, and indurated ulcer) w/ enlarged lymph nodes



**Figure 5-9.** Secondary syphilis. A classic presentation for secondary syphilis with copper-colored scaly plaques on the palms and soles. (From Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 6th edn. Elsevier, 2015.)

- **Secondary** (3–10 weeks postchancere; dissemination to other tissues; clears in 3–12 weeks, but relapses in 25%)
  - Prodromal signs (e.g., malaise, fever, lymph node enlargement, and arthralgia)
  - Papulosquamous/maculopapular generalized rash (“copper colored”) w/ papules/plaques on palms/soles (Fig. 5-9)
  - “Moth eaten” alopecia
  - Split papules (syphilitic perlèche)
  - Mucous patches in oropharynx (condyloma lata-like lesions of the mouth)
  - Hypopigmented macules on neck (“necklace of Venus”)
  - Condyloma lata
- **Tertiary** (months to years after secondary – the period in between is called latency)
  - Gummas (skin, bones, liver, and organs)
  - Cardiovascular syphilis (e.g. aortitis)
  - Neurosyphilis (e.g., paresis, meningitis, ataxia, tabes dorsalis, optic atrophy, gummas, and Argyll-Robertson pupil (accommodates to light, but does not react))
- Treatment: IM **benzathine PCN** (2.4M IU ×1 dose for primary/secondary/early latent disease; 7.2M IU total for late latent disease)
- Other high-yield facts:
  - M > F, ↑in MSM
  - ↑risk of coinfection w/ HIV (any disease that → genital ulcers will increase HIV risk)
  - HIV → ↑risk of neurosyphilis
  - Serologic studies are divided into **Treponemal** (FTA-ABS, MHA-TP) and **Non-treponemal** (RPR, VDRL); most sensitive and specific tests are FTA-ABS and MHA-TP
  - **RPR and VDRL**: first serologic test to become positive (within 1-2 weeks vs after 3rd week for Treponemal tests); used to monitor response to therapy as titers decrease and then become negative after successful treatment (vs Treponemal tests, which remain positive throughout life); **higher false positive rate** than Treponemal tests (esp. pregnancy and SLE)
  - Warthin-Starry stain identifies spirochetes
  - Positive darkfield examination (overall most sensitive and specific test for diagnosis of **primary** syphilis)
  - Histology of secondary syphilis: **slender, elongated psoriasiform** epidermal hyperplasia + lichenoid interface changes + “dirty” dermal inflammatory infiltrate (neutrophils, cell debris, and **abundant** plasma cells)

## Other bacterial venereal diseases (see Table 5-10)

### V. Mycobacterial infections

#### Cutaneous tuberculosis

- *Mycobacterium tuberculosis* = acid-fast, alcohol-fast, aerobic bacillus, and ↑risk in HIV
- Diagnosis made with tuberculin skin test vs interferon-γ release assays (QuantiFERON® Gold)
  - Skin test better in children; interferon-γ test better for patients who have had BCG (live, attenuated *M. bovis*) vaccination (false (+) with skin test)
- **Inoculation-induced**
  - Tuberculous chancre: in patients w/o previous infection (hence **no immunity** against TB); 2 to 4 week inoculation period; painless, red, and indurated papule that ulcerates – heals after 3 to 12 months; may spread to lymph nodes
  - **Tuberculosis verruca cutis**: reinfection via inoculation, in patients w/ previous infection w/ moderate-to-high immunity; #1 form of cutaneous TB; **warty/verrucous**, growing papule may heal over years
- **Spread of endogenous infection**
  - **Lupus vulgaris**: contiguous spread or hematogenous/lymphatic; red-brown, sometimes annular, papules/plaques (with “apple jelly” color on diascopy) that → scarring centrally; head/neck #1 site; **moderate-to-high immunity**
  - **Scrofuloderma**: result of contiguous spread of infection to skin from underlying disease (usually **cervical lymph nodes** and bones); fluctuant nodules that develop sinus tracts, draining to skin, with tethered appearance; **low immunity**
  - **Orificial tuberculosis**: patients with advanced TB and poor cell-mediated immunity; **autoinoculation of mucosa/skin** close to anatomic orifice draining active systemic TB infection → ulceration/drainage
  - **Acute miliary tuberculosis**: hematogenous dissemination from lung, most often in **immunosuppressed pts**; **pinpoint blue-red crusty papules** → small scars
  - **Tuberculous gumma**: hematogenous dissemination → deep nodule that ulcerates/drains; immunosuppressed pts
- First-line combination therapy for TB: **rifampin, isoniazid, pyrazinamide, and ethambutol**

**Table 5-10.** Venereal Diseases Other Than Syphilis

Disease	Organism	Dermatologic Signs	Treatment	Interesting Facts
Chancroid	<i>Hemophilus ducreyi</i> (Gram(-) coccobacilli)	<b>Painful</b> , purulent ulcers with <b>ragged/undermined</b> borders and fibrinous base (may get 'kissing ulcers' from apposition of skin with initial ulcer) Prepuce/coronal sulcus/frenulum are common sites Painful inguinal lymphadenitis (40%)	<b>Azithromycin</b> 1 gm PO × 1 dose	' <b>School of fish</b> ' sign on Giemsa stain of exudate smear M > F; <b>prostitutes</b> are major reservoir
Gonorrhea	<i>Neisseria gonorrhoeae</i> (Gram (-) diplococci)	Most findings are not cutaneous, but can get <b>hemorrhagic acral pustules w/arthritis</b> (of larger joints), and fever (arthritis-dermatosis syndrome) if hematogenous dissemination occurs	<b>Dual therapy:</b> Ceftriaxone 250 mg IM ×1 dose + Azithromycin 1 gm PO × 1 dose	F > M Culture is gold standard for diagnosis ( <b>Thayer-Martin</b> media is used) Often see <b>coinfection w/ chlamydia</b>
Lymphogranuloma venereum	<i>Chlamydia trachomatis</i> (serotypes L1–3)	<b>Stage 1</b> (after 3–12d incubation period): painless ulcer which resolves (transient) +/- lymphangitis <b>Stage 2</b> (10–30 days, up to 6 months after stage 1): <b>buboes</b> (unilateral, painful, erythematous, and enlarged inguinal lymph nodes) w/ ' <b>groove sign</b> ' (enlarged nodes above and below Poupart ligament); buboes may rupture → pus drainage and sinus tracts <b>Stage 3</b> (months-years after stage 2; aka ano-genito-rectal syndrome): <b>proctocolitis</b> w/ perirectal abscesses, fistulas, strictures/stenoses, and 'lymphorrhoids' (perirectal/intestinal lymphatic hyperplasia)	<b>Doxycycline</b> 100 mg PO BID × 21 days	' <b>Gamma-Favre bodies</b> ' in macrophages on Giemsa stain More common in Asia, Africa, and South America <b>M &gt; F</b>
Granuloma inguinale	<i>Klebsiella granulomatis</i> (Gram-negative bacillus)	Enlarging chronic <b>painless ulcer</b> with ' <b>beefy red</b> ,' friable, hypertrophic <b>granulation tissue</b> (avg incubation = 17 days) Get 'pseudobuboes' (nodules), genital swelling, and secondary infections (→ bad odor) Most common sites: prepuce/glans/frenulum/coronal sulcus (men); vulvar area (women) May get extragenital lesions as a result of dissemination or autoinoculation (skin, bones, oral, and abdominal)	<b>Azithromycin</b> 1 gm PO once weekly (or 500 mg daily) for at least 3 weeks AND until all lesions have resolved	' <b>Safety pin</b> ' <b>Donovan bodies</b> on Wright or Giemsa stain of smears India, Papua New Guinea, Australia, and South Africa

**Table 5-11.** Polar and Borderline Leprosy

Clinical Findings	Lepromatous (LL)	Borderline (BB)	Tuberculoid (TT)
Type of lesions	Small hypopigmented macules, papulonodules, and <b>diffuse infiltration</b> (→ <b>leonine facies</b> , elongated earlobes, and madarosis)	Plaques and dome-shaped lesions	<b>Dry, scaly, hypopigmented, and anesthetic plaques</b> with raised peripheral rim and central atrophy +/- alopecia and anhidrosis
Lesion number/size	<b>Innumerable, small</b>	Multiple (but countable); variable sizes	<b>One or few</b> (<5); large
Distribution	<b>Widespread</b>	Generalized but asymmetric	<b>Localized, asymmetric</b>
Circumscription	<b>Poorly defined</b> lesions and difficult to discern edges	Not as sharply defined as TT	<b>Well-defined</b> ; sharply demarcated raised/indurated borders
Sensation within lesions	<b>Normal</b>	↓	<b>Absent</b>
Site of nerve enlargement	Symmetric and <b>not a/w skin lesions</b>	Variable	Asymmetric and <b>localized around skin lesions</b>
Lepromin test	Negative	+	+++
Cell-mediated immunity	None ( <b>Th2</b> >> Th1)	Unstable	<b>Strong</b> ( <b>Th1</b> >> Th2)
Bacilli in skin lesions	++++ ( <b>globi</b> )	++	None
AFB stain (Fite-Faraco stain is best)	++++	++	<b>Negative</b>
Histology	<b>Grenz zone</b> , diffuse infiltrate of <b>parasitized foamy histiocytes (Virchow cells)</b> , free-floating <b>clumps of bacilli (globi)</b> in dermis, and "onion-skin" pattern around nerves; lacks well-formed granulomas	Overlap of LL and TT findings, organisms easily seen	Well-formed sarcoidal <b>granulomas w/linear arrangement (East-West) along nerves</b> , numerous Langhans giant cells, fragmented nerve fibers, lacks organisms (no globi or Virchow cells), and Grenz zone
Associated findings	Acquired ichthyosis, <b>madarosis</b> , <b>saddle nose</b> , lagophthalmos, and orchitis (→ sterility and gynecomastia)		
Other comments	<b>High risk for type 2 reaction</b> Lesions do not have anhidrosis or alopecia	Borderline categories (BL, BB, and BT) are <b>highest risk for type 1 reactions</b> BL is high risk for type 2 reaction	Skin lesions favor face, extremities, and cool areas of trunk TT often self resolves in 3 years



## Leprosy (Hansen's disease)

- Agent: *Mycobacterium leprae*
  - Obligate intracellular, weakly acid-fast bacillus that parasitizes macrophages and Schwann cells
  - Requires cool temperatures (30°C–35°C) for growth → predilection for cooler areas of skin (nose, testes, and ear lobes) and peripheral nerves that lie close to skin surface
  - Transmitted primarily by nasal/oral droplets; also 9-banded armadillos in the southeast United States
  - Cannot be cultured *in vitro* → must be cultivated in mouse footpads or in armadillos
- Chronic, deforming disease characterized by skin and nerve involvement
- Prolonged incubation period (avg 4–10 years, but up to 30 years!); bimodal age range (10–15 years old and 30–60 years old); M > F
- Characterized by granulomas and neurotropism, both within skin and peripheral nerves
- Primary skin lesion = erythematous, or hypopigmented, annular plaque w/ mild scaling
- Peripheral nerves are enlarged in all forms (except indeterminate)
  - Most commonly affects superficially located nerve trunks (CN-5, CN-7, median, radial, ulnar, greater auricular, posterior tibial, and common peroneal nerves)
  - Damage results in: “claw hand” and “pupal hand” flexural deformities, stocking-glove anesthesia, neuropathic ulcers of plantar surfaces, foot drop, atrophy of interosseous muscles, and ocular damage (because of CN-7 dysfunction)
- *M. leprae*-specific cell-mediated immunity (assessed by lepromin skin test) plays a major role in the Ridley-Jopling scale → divides leprosy into two polar forms (Lepromatous/LL (Th2 response) and Tuberculoid/TT (Th1 response), and three borderline forms (BL, BB, and BT) (see Table 5-11)
  - Polar forms are stable! → patients in either polar form (LL or TT) remain in this form throughout their disease course
  - Borderline forms are unstable and have clinicopathologic features somewhere in between the polar forms
- Indeterminate leprosy (earliest stage of leprosy): p/w solitary, ill-defined hypopigmented macule, without enlargement of peripheral nerves
  - Disease will either self-resolve, or evolve into one of five leprosy forms (LL, BL, BB, BT, or TT)
- Reactional states: abrupt-onset skin lesions that arise in 50% of patients during or after initiation of therapy
  - Type 1 (reversal reaction): result of change in cell-mediated (Th1) immunity against *M. leprae*. May either be downgrading (borderline leprosy pt who “downgrades” toward lepromatous pole) or upgrading (increase in cell-mediated immunity). Both may p/w ulceration of existing lesions and preferential targeting of nerves, resulting in dangerous neuritis (= emergency!); generally lacks

systemic symptoms (unlike Type 2 reactions); highest risk with Borderline forms (BL > BB, BT); Treatment = prednisone

- Type 2 (erythema nodosum leprosum): Th2 (humoral)-mediated formation of immune complexes, resulting in multisystem vasculitis and EN-like lesions scattered at previously unaffected skin sites (medial thighs and extensor forearms are #1 sites); prominent systemic symptoms; highest risk with LL and BL forms; Treatment = thalidomide
- Lucio phenomenon: severe necrotizing vasculitis w/ thrombosis; only occurs in patients from western Mexico with diffuse lepromatous leprosy; p/w purpuric macules and ulcerative bullous lesions below the knees; Treatment = prednisone
- Treatment (WHO recommendations):
  - Multibacillary (duration = 12 months): rifampicin 600 mg Qmonth + dapsone 100 mg QD + clofazimine 300 mg once a month and 50 mg daily
  - Paucibacillary (duration = 6 months): rifampicin: 600 mg Qmonth + dapsone 100 mg QD
  - Single skin lesion paucibacillary leprosy (duration = single dose): rifampicin 600 mg + ofloxacin 400 mg + minocycline 100 mg

## Atypical mycobacteria

- *Mycobacterium avium* complex: more commonly seen in AIDS patients; found in environment (water, soil, and animals); pulmonary infection is most common finding; skin findings w/ primary inoculation or via dissemination (pustules, ulcers on legs, and nodules); ↑alkaline phosphatase; clarithromycin/azithromycin + ethambutol +/- rifampin
- *Mycobacterium marinum*: acquired via cutaneous contact (usually hands w/ abrasions) with aquatic environments (e.g., fish tanks and swimming pools) → erythematous/blue ulcerating nodules in a sporotrichoid pattern; Diagnosis is confirmed with culture: *M. marinum* grows best at 31 degrees Celsius (~3 weeks required for growth), as opposed to the usual 37 degrees for most other mycobacteria; tx: clarithromycin +/- rifampin/ethambutol, minocycline, and TMP-SMX
- *Mycobacterium ulcerans*: aka Buruli ulcer; usually in Africa, in areas close to water bodies; nodule → ulcer on extremities; can become >15 cm and extend to bones; tx: excision (treatment of choice), local heating, rifampin + streptomycin, and amputation
- *Mycobacterium fortuitum*, *chelonae*, and *abscessus*: rapid growing mycobacteria (Table 5-12); saprophytic organisms; can get infections posttrauma/surgery or medical treatments (e.g., implant placement, liposuction, and botulinum toxin)/tattoo/nail salon footbaths; skin presentations vary, but most common is inflamed subcutaneous nodules in sporotrichoid pattern; clarithromycin is treatment of choice, but surgical tx may be needed

## 5.4 FUNGAL DISEASES

### I. Superficial mycoses

#### Dermatophytes

- Species – three genera: *Microsporum*, *Epidermophyton*, and *Trichophyton*
  - Generally cause superficial skin infections and nail infections
  - The most common organism(s) that cause(s) various manifestations are as follows (very HIGH-YIELD for Boards!!!):
    - Tinea capitis** – *Trichophyton tonsurans* (#1 cause in United States), *Microsporum canis* (#1 cause worldwide; more inflammatory), and *T. violaceum* (East Africa)
      - Endothrix (black dot; arthroconidia within hair shaft)**: *T. rubrum*, *T. tonsurans*, *T. schoenleinii*, *T. yaounde*, *T. violaceum*, *T. gourvillii*, and *T. soudanense* (Mnemonic: “Ringo Gave Yoko Two Squeaky Violins”)
      - Ectothrix (arthrospores around hair shaft)**
        - Fluorescent (via Wood lamp – pteridine): *M. canis*, *M. audouinii* (formerly #1 cause in children), *M. gypseum*, *M. ferrugineum*, *M. distortum*, and *T. schoenleinii* (Mnemonic: “Cats And Dogs Fight and Growl Sometimes”)
        - Nonfluorescent: *T. mentagrophytes*, *T. rubrum*, *M. nanum*, *M. megninii*, *T. gypseum*, and *T. verrucosum*
    - Favus** – *T. schoenleinii* > *M. gypseum*, *T. violaceum*
    - Kerion** – *M. canis*, *T. verrucosum*, *T. mentagrophytes*, and *T. tonsurans*

**Table 5-12.** Mycobacteria That Cause Cutaneous Disease

Mycobacteria That Cause Cutaneous Disease		
Group and pigment	Rate of growth	Pathogens
<b>Slow growers</b>		
Photochromogens*	2–3 weeks	<i>M. kansasii</i> , <i>M. marinum</i> , <i>M. simiae</i>
Scotochromogens†	2–3 weeks	<i>M. scrofulaceum</i> , <i>M. szulgai</i> , <i>M. goodii</i> , <i>M. xenopi</i>
Nonchromogens‡	2–3 weeks	<i>M. tuberculosis</i> , <i>M. avium</i> , <i>M. intracellulare</i> , <i>M. ulcerans</i> , <i>M. haemophilum</i> , <i>M. malmoense</i> , <i>M. terrae</i> , <i>M. genavense</i> , <i>M. bovis</i> §, <i>M. nonchromogenicum</i>
<b>Rapid growers</b>	3–5 days	<i>M. fortuitum</i> , <i>M. chelonae</i> , <i>M. smegmatis</i> , <i>M. abscessus</i> , <i>M. immunogenum</i> , <i>M. goodii</i> , <i>M. wolinskyi</i> , <i>M. cosmeticum</i> , <i>M. mucogenicum</i>
<b>Non-cultured (to date)</b>		<i>M. leprae</i>

\*Capable of yellow pigment formation upon exposure to light.

†Capable of yellow pigment production without light exposure.

‡Incapable of pigment production.

§Including bacillus Calmette-Guérin. Modified classification of Runyon.

- Majocchi granuloma** – *T. rubrum* most common
- Tinea corporis** – *T. rubrum* most common
  - ◆ Zoophilic species (i.e., in farmers and pets) – *T. verrucosum* and *M. canis*
- Tinea imbricatum** – *T. concentricum*
- Tinea barbae** – *T. verrucosum*, *T. mentagrophytes*, *T. tonsurans*, and *T. rubrum*
- Tinea faciei** – usually zoophilic species (*M. canis* and *T. mentagrophytes*) > *T. rubrum*; most commonly in kids after visiting rural areas
- Tinea cruris** – *T. rubrum* > *E. floccosum* and *T. interdigitale*
- Tinea pedis**
  - ◆ Moccasin and interdigital – *T. rubrum* > *E. floccosum* (moccasin), *T. interdigitale* (interdigital)
  - ◆ Vesicular/bullous – *T. mentagrophytes*
- Onychomycosis**
  - ◆ Distal subungual: *T. rubrum*, *T. interdigitale*, and *E. floccosum*
  - ◆ Proximal white subungual – *T. rubrum*
    - ↑risk in HIV
  - ◆ White superficial – *T. mentagrophytes* (adults) vs *T. rubrum* (children)
  - ◆ Less common causes: *C. albicans* (most commonly in setting of mucocutaneous candidiasis), *Fusarium* spp. (white superficial onychomycosis), *Scytalidium* spp. (dark onychomycosis with chronic paronychia), and *Scopulariopsis brevicaulis* (white superficial onychomycosis)
- Geography** – ubiquitous; fungi are classified according to their normal habitat:
  - Anthropophilic**: restricted to humans and cause a chronic, mild inflammatory response; includes all *Trichophyton* spp. (except *T. mentagrophytes* and *T. verrucosum*), *E. floccosum*, *M. audouinii*, and *M. ferrugineum*
  - Zoophilic**: primarily affect animals; cause massive inflammatory response in humans; includes *M. canis* (cats and dogs), *M. nanum* (pigs), *T. verrucosum* (cattle), and *T. mentagrophytes* (rodents)
  - Geophilic**: found in soil; cause severe inflammatory response and scarring in humans; *M. gypseum* (soil) is the only common species in this class
- Histology** – septate hyphae in stratum corneum or nail plate, **brisk dermal inflammation** (vs minimal in tinea versicolor) +/- neutrophilic microabscesses in epidermis or corneum/nail plate
  - PAS (red) and GMS (black)
- Diagnosis** – KOH (helps break down keratin making fungi more visible) +/- culture
  - Chlorazol black E – **chitin stain** – hyphae will be green
  - Calcofluor white – chitin stain – blue or green with **fluorescence** microscopy
- Pathogenesis**: virulence factors (hydrolases and keratinases) allow penetration into stratum corneum and the released enzymes induce inflammation (Th1 response)
- Clinical presentation**:
  - *Tinea corporis/cruris*: annular scaly patches/plaques with inflamed and possibly palpable borders;
  - *tinea cruris* spares scrotum (unlike candidiasis)

- Tinea pedis/manuum: erythema with scale, especially between toes (maceration) and sides of feet
- Tinea capitis: circular scaling patches +/- pustules +/- **lymphadenopathy**; may have black dots from broken hairs in endothrix infections; treat with systemic antifungals
  - ◆ Usually school age children; ↑ in blacks/males
  - ◆ Kerion: boggy inflamed nodule/abscess with pustules and possible lymphadenopathy which may → scarring
  - ◆ Favus: yellow cup-shaped crusts (**scutula**) that cluster together, resulting in a honeycomb appearance and can → scarring
  - ◆ Green fluorescence of infected hairs with Wood lamp may be seen with *Microsporum* infection
- Tinea imbricatum: concentric and **polycyclic** rings of scale
- Majocchi's granuloma: erythematous papules/nodules around hair follicles, particularly lower legs (may arise from tinea pedis); systemic antifungals needed for treatment
- Tinea faciei: erythematous follicular-based papules, often in an annular distribution most common in kids; treat with systemic antifungals
- Treatment: topical or systemic terbinafine or azole antifungals, topical naftifine
  - Terbinafine and griseofulvin have equivalent safety/efficacy in children in the treatment of tinea capitis; **terbinafine more effective for *T. tonsurans*** and **griseofulvin more effective for *Microsporum***

### Tinea versicolor (pityriasis versicolor)

- Species: *Malassezia globosa* and *M. furfur*; yeast form is normal skin flora; transforms to filamentous/hyphal form in disease states; culture requires **olive oil** for growth
- More common in darker skin/adolescents/summer
- Histology: hyphae and spores ("**spaghetti and meatballs**") seen in stratum corneum (also on KOH)
- Pathogenesis: overgrowth of normal flora, which is ubiquitous (esp. with warmth and humidity in the right host); **hypopigmentation** due to **melanocyte inhibition by azelaic acid** (dicarboxylic acid byproduct of *Malassezia*)
- Clinical presentation: hyper- or hypopigmented finely scaling circular/oval macules/patches in sebaceous distribution (scalp, face, neck, upper chest, and upper back)
- Treatment: topical or systemic **azole-antifungals**, selenium sulfide shampoo, or topical ciclopirox

### Piedra

- Species:
  - Black – *Piedra hortae*
  - White – *Trichosporon asahii* (most strongly linked to white piedra; formerly, *T. beigeli*; may cause **disseminated disease in immunocompromised pts**), *T. ovoides*, *T. inkin*, and *T. cutaneum*
- Geography: tropical
- Pathogenesis: found in water and soil in tropics
- Microscopy: black or white **concretions along hair** (encircle hairs, unlike the sac-like appearance of lice)

- **White piedra with soft mobile nodules; black piedra with hard nonmobile nodules**
- Clinical presentation: asymptomatic hair breakage on scalp, axillary, and pubic region
- Treatment: **hair shaving/cutting** and antifungal shampoos; systemic antifungals if recalcitrant

### Tinea Nigra

- Species: *Hortaea werneckii*
- Geography: tropical and subtropical, especially coastal
- Microscopy: dark brown septate hyphae with budding yeast in thickened stratum corneum
- Pathogenesis: overgrowth of fungus
- Clinical presentation: dark-brown/**black macule or small patch on palms/soles**, limited to stratum corneum
- Treatment: azole creams, Whitfield's ointment; oral terbinafine if recalcitrant

## II. Subcutaneous mycoses

### Sporotrichosis

- Species: *Sporothrix schenckii*
- Geography: **ubiquitous saprophyte**; endemic to Central/South America and Africa
- Microscopy: usually not well-visualized with stains; granulomatous inflammation with plasma cells and asteroid corpuscles (Splendore-Hoeppli phenomenon); organisms are **cigar-shaped budding yeast**
- Pathogenesis: traumatic inoculation from soil via plant thorns, **wood splinters, and sphagnum moss** >> cats/rodents/armadillo bites; inhalation of spores
- Clinical presentation: **multiple ascending ulcerated nodules** or subcutaneous abscesses, most frequently in gardeners, agriculture/farm workers, and veterinarians
  - May → erythema nodosum
- Treatment: obtain fungal culture (difficult to find in tissue samples), **itraconazole (treatment of choice)**, SSKI, and amphotericin B in disseminated disease
- Sporotrichoid spread mnemonic: **Nocardia, Sporotrichosis, Atypical mycobacteria, Leishmaniasis, Tularemia (No SALT)**

### Lobomycosis

- Species: *Lacazia (Loboa loboi)*
- Geography: infects **freshwater dolphins** in South American Rivers
- Microscopy: thick-walled yeast with tubular connections between cells – "**pop bead**" or "**chain of coins**" appearance
- Pathogenesis: unable to be cultured in vitro
- Clinical presentation: **keloid-like verrucous fibrotic nodules** that can ulcerate; men >> women; rural areas
- Treatment: **surgical excision**

### Mycetoma

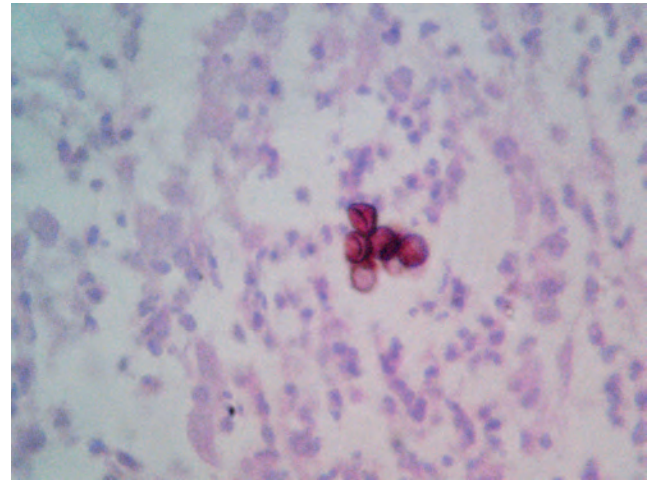
- Species:
  - **Eumycetoma (fungus)** – *Madurella* spp. *Pseudallescheria boydii* (most common), *Exophiala jeanselmei*, and *Acremonium* spp.





**Figure 5-10.** Mycetoma cases produced by *N. brasiliensis*. (A) Inflammation of the dorsum of the foot and ankle showing abscesses and sinuses. (B) Mycetoma of the back of the neck. (From Welsh O, Vera-Cabrera L, Salinas-Carmona MC. Mycetoma. Clinics in Dermatology 25:2:195–202 Elsevier, 2007.)

- **Actinomycetoma (bacteria)** – *Nocardia* (*N. brasiliensis* [#1 bacterial cause] and *N. asteroides* both have **white grains**), *Actinomadura* spp. (*A. pelletieri* = **red grains**; *A. madurae* = cream or pink grains), and *Streptomyces somaliensis* (**yellow-brown grains**)
- Geography: southern tropics (Latin America, India, and Africa), a/w poverty and bare feet; young men
- Microscopy: granulomatous reaction with grains; serologic testing used because of culture difficulty
- Pathogenesis: traumatic inoculation
- Clinical presentation (Fig. 5-10): slow progression of tumors with **sinus tracts draining grains**, which are fungal or bacterial aggregates; most common on **feet/lower legs**; long-standing lesions → bone and visceral involvement
  - **Black grains only seen in eumycetoma and red grains only seen in actinomycetoma** (specifically *A. pelletieri*); other colored grains seen in both types
- Treatment:
  - Actinomycetoma: sulfonamides and other antibacterial agents
  - Eumycetoma: surgical debridement and several month courses of azole antifungals



**Figure 5-11.** Fumagoid cells, or sclerotic or Medlar bodies. (H&E, original magnification 40x) (From Torres-Guerrero E, Isa-Isa R, Isa M, Arenas R. Chromoblastomycosis in Clinics in Dermatology, 30:4:403–408 Elsevier, 2012.)

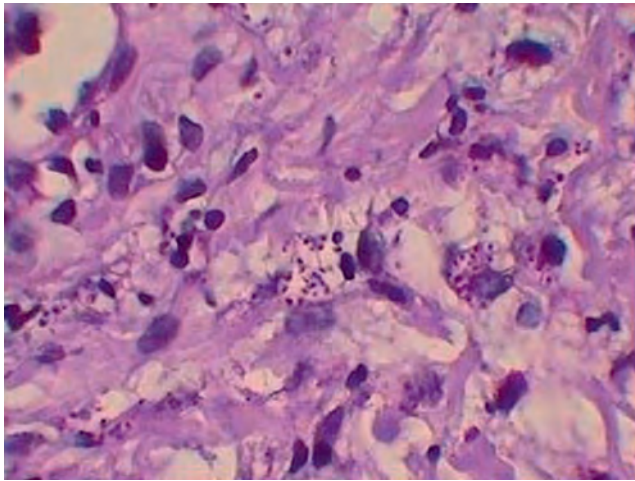


**Figure 5-12.** Chromoblastomycosis, facial lesions. (From Torres-Guerrero E, Isa-Isa R, Isa R, Arenas R. Chromoblastomycosis in Clinics in Dermatology, 30:4:403–408 Elsevier, 2012.)

## Chromoblastomycosis

- Species: *Fonsecaea pedrosoi* (most common), *Rhinocladiella*, *Phialophora verrucosa*, and *Cladophialophora carrionii*
- Geography: tropical and subtropical climates; found in decaying vegetation and soil
- Microscopy (Fig. 5-11): pseudoepitheliomatous hyperplasia, granulomatous dermal inflammation with **medlar bodies** (pigmented muriform cells, “**copper pennies**”)
- Pathogenesis: traumatic inoculation by thorns or splinters
- Clinical presentation (Fig. 5-12): weeks to months after inoculation, pruritic papules/nodules that expand and





**Figure 5-13.** Histoplasmosis. Biopsy specimen shows periodic acid Schiff-positive intracellular yeast. (From Chang P, Rodas C. Skin lesions in histoplasmosis in *Clinics in Dermatology* 30:6:592–598 Elsevier, 2012.)

become verrucous with black dots; does not invade muscle or bone; chronic lesions can → SCC

- Treatment: itraconazole, 5-flucytosine, among other antifungals; surgical excision for small lesions

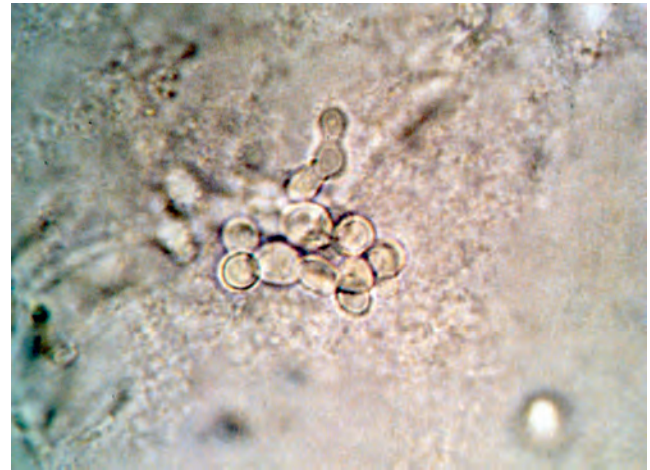
### III. Systemic (dimorphic) mycoses

#### Histoplasmosis

- Species: *Histoplasma capsulatum* var. *capsulatum*
  - African: *Histoplasma capsulatum* var. *duboisii*
- Geography: Ohio and Mississippi River valley
- Microscopy (Fig. 5-13): tuberculoid granuloma with intracellular 2–4  $\mu\text{m}$  yeast in histiocytes (looks like leishmaniasis, but see yeast have surrounding halo and are more evenly distributed throughout histiocyte cytoplasm; lacks “marquee sign” and kinetoplast)
- Pathogenesis: inhalation (esp. bird and bat feces) with hematogenous spread (can go to liver, spleen, bone marrow, and brain; skin involvement more common in HIV, often p/w umbilicated or “molluscoid” papules)
- Clinical presentation: primary cutaneous chancre with lymphangitis and lymphadenitis (rare); more commonly, secondary cutaneous molluscoid nodules, cellulitis, ulcers, panniculitis, and oral lesions
  - Pulmonary manifestations = most common presentation
- Treatment: Itraconazole (mild-moderate disease), or amphotericin B (severe disease)

#### Blastomycosis (“North American blastomycosis”)

- Species: *Blastomyces dermatitidis*
- Geography: Eastern United States (esp. SE), Great Lakes, Ohio, and Mississippi River valleys
- Microscopy (Fig. 5-14): pseudoepitheliomatous hyperplasia, granulomatous dermal inflammation with unipolar budding yeast (8–18  $\mu\text{m}$ ) (broad-based buds)



**Figure 5-14.** Blastomycosis. Direct microscopy of a blastomycosis case; budding yeast with a wide fusion base are seen (original magnification 400x). (From López-Martínez R, Méndez-Tovar LJ. Blastomycosis in *Clinics in Dermatology* 30:6:565–572 Elsevier, 2012.)

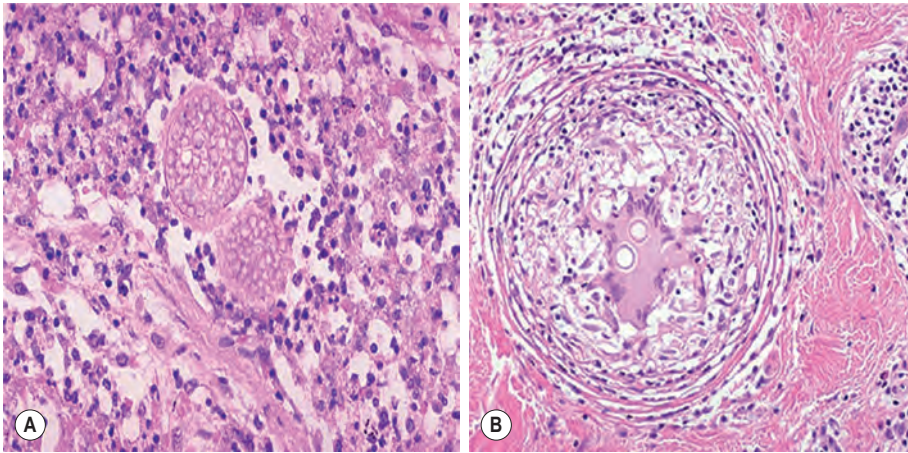
- Pathogenesis: inhalation with subsequent hematogenous spread to skin (>75% of cases), bones, and genitourinary tract (e.g., prostate, spleen, liver, and brain)
- Clinical presentation: primary cutaneous form (rare) presents with lymphangitis and lymphadenitis at injury site; secondary cutaneous form (more common; due to hematogenous dissemination from lungs to skin), presents with verrucous nodules, abscesses, and ulcers (can occur orally as well)
  - Pulmonary manifestations = most common presentation
- Treatment: polyene and azole antifungals (mainly itraconazole) and amphotericin B (severe disease)

#### Coccidioidomycosis

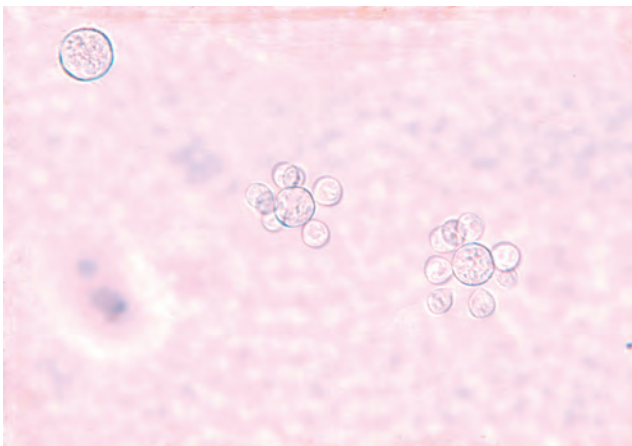
- Species: *Coccidioides immitis*
- Geography: desert Southwest United States (esp. Central Valley/San Joaquin Valley, California), Mexico, and Central/South America
- Microscopy (Fig. 5-15): large (up to 100  $\mu\text{m}$ ) spherules containing endospores; also has PEH and granulomatous inflammation
- Pathogenesis: inhalation with hematogenous spread to skin (as well as CNS and bone); very rarely primary cutaneous infection
- Clinical presentation: verrucous nodules/papules, pustules, abscesses, or ulcerative lesions
  - Pulmonary manifestations = most common presentation
- Treatment: limited and cutaneous: itraconazole; severe: amphotericin B; meningial: amphotericin B and fluconazole

#### Paracoccidioidomycosis (“South American Blastomycosis”)

- Species: *Paracoccidioides brasiliensis*
- Geography: southern United States, Mexico, and Central/South America



**Figure 5-15.** Coccidioidomycosis. Granulomas show large spherules and a giant cell containing small spherules (H&E; original magnification 400x). (From Welsh O, Vera-Cabrera L, Rendon A, Gonzalez G, Bonifaz A. Coccidioidomycosis in Clinics in Dermatology 30:6:573–591 Elsevier, 2012.)



**Figure 5-16.** Paracoccidioidomycosis. Direct examination of sputum showing *P. brasiliensis*. (10% KOH, 400x). (From Ramos-e-Silva M, Lima CMO, Schechtman RC, Moritz-Trope B, Carneiro S. Systemic mycoses in immunodepressed patients (AIDS) in Clinics in Dermatology 30:6:616–627 Elsevier, 2012.)

- Microscopy (Fig. 5-16): Pseudoepitheliomatous hyperplasia, granulomatous dermal inflammation with multipolar budding yeast (**mariner's wheel**)
- Pathogenesis: inhalation of infected soil (can disseminate to skin, liver, adrenal glands, lymph nodes, gastrointestinal tract, and spleen); rarely may arise from direct inoculation in skin
- Clinical presentation: granulomatous ulcerative **oropharyngeal and perioral** involvement in 70% of adults; cutaneous lesions can be contiguous, hematogenous, or via inoculation; clinical appearance of ulcers with infiltrated borders and hemorrhagic dots, and associated lymphadenopathy (can be massive)
  - Men >>> women
  - Pulmonary disease (granulomatous and chronic) most common presentation
- Treatment: mild: TMP/SMX; moderate: itraconazole; meningial: fluconazole or voriconazole; and severe: amphotericin B

## IV. Opportunistic systemic mycoses

### Candidiasis

- Species: *C. albicans* (most common in systemic and localized infections), *C. tropicalis* (also very common; in systemic infection, frequently disseminates to skin), *C. parapsilosis* (commonly seen in chronic paronychia), *C. glabrata* (fluconazole resistance), *C. krusei* (fluconazole resistance), and *C. dubliniensis* (oropharyngeal candidiasis in HIV patients)
- Geography: ubiquitous
- Microscopy: KOH = **yeast and pseudohyphae**
- Pathogenesis:
  - Candida species form biofilm on plastic medical devices
  - SAPs (secretory aspartyl proteinases) and phospholipases aid in fungal adhesion and tissue invasion
  - Chitin, mannoprotein and glucan may function as adhesins, which allow candida to adhere to mucosal surfaces
  - *C. albicans* exists in normal flora of skin and digestive/genitourinary tracts with pathologic state with immunosuppression, and debilitation and imbalances in microbiome
- Clinical presentation:
  - **Mucocutaneous candidiasis:** vaginal candidiasis, **oral thrush** ("cottage cheese" like), **median rhomboid glossitis** (central smooth erythema of tongue), **onychomycosis**, **chronic paronychia** (not always involved but often), **candidal intertrigo** (typically see beefy red color + satellite pustules +/- erosions), **angular cheilitis** (perlèche; RFs: edentulous, elderly, atopic dermatitis, and vitamin deficiencies), and **erosio interdigitalis blastomycetica** (third web space of fingers; also 4th web space of toes)
    - RFs: DM2 and corticosteroids/immunosuppression (if chronic/severe may be sign of HIV)



- **Deep-seated candidiasis:** usually starts in GI tract; 10% of bloodstream infections; 30% mortality in systemic candidiasis despite antifungal therapy
  - Usually in immunosuppressed patients who are neutropenic
  - See scattered papules/nodules, occ. hemorrhagic and ecthyma gangrenosum-like
  - Also infect muscles, retina, internal organs, and heart valves
- Treatment:
  - Mucocutaneous: polyenes (e.g., Nystatin) and azole preparations (e.g., clotrimazole and fluconazole)
    - *C. glabrata* and *krusei* have lower sensitivity to azole antifungals; *C. albicans* is developing resistance to fluconazole
  - Systemic: amphotericin B, azoles, and echinocandins

## Cryptococcosis

- Species: *C. neoformans* and *C. gattii*
- Geography: in bird droppings (particularly **pigeons**) and bark/fruit of tropical trees; *C. neoformans* – ubiquitous, *C. gattii* – tropical, subtropical
- Microscopy: single-celled sphere with a double cell wall and **thick capsule** (“halo” appearance), may have one or more buds (blastoconidia); collections of organisms look like **soap bubbles**
  - Stains: **India ink**, **PAS**, **mucicarmine**, **GMS**, and Fontana-Masson
- Pathogenesis: inhalation → lungs (1° pulmonary infection, usually mild) → hematogenous spread (CNS, bones, and skin); can also arise from primary inoculation of skin (rare)
  - More common in immunosuppressed individuals (esp. in **HIV/AIDS**, but also associated with sarcoidosis and pregnancy)
  - Glucuronoxylomannan polysaccharide capsule is a virulence factor
- Disease manifestation
  - **Papules/nodules (often molluscum-like)** that can be **umbilicated** and/or ulcerated, and prefer **head/neck, mouth, and nose**
    - Patients with 2° cutaneous lesions have high mortality rate
  - Nodular lymphangitic syndrome – nodule at inoculation site, nodular lymphangitis, and adenopathy
  - **Meningoencephalitis** is a serious and common manifestation
- Treatment – mild: **oral fluconazole**, CNS: amphotericin B and flucytosine

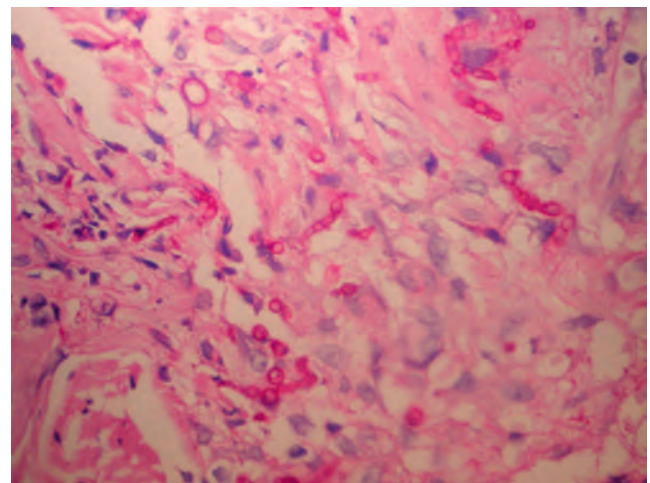
## Aspergillosis

- Species: *Aspergillus fumigatus* most common, *A. flavus* (second most common), and *A. niger* (can → otomycosis)
- Geography: ubiquitous in soil
- Microscopy (Fig. 5-17): **septate hyphae with 45° angle branching**

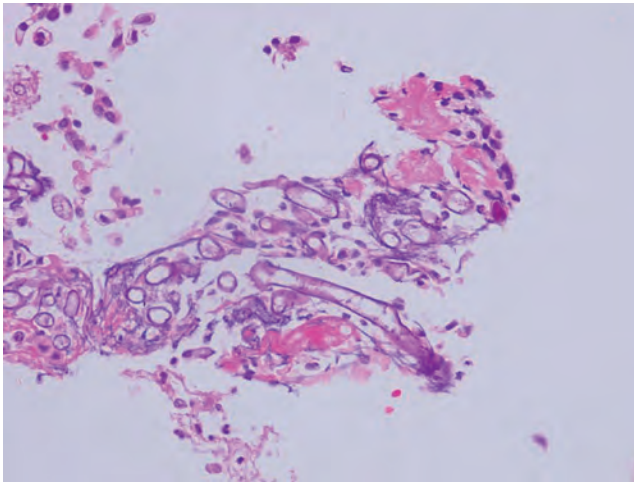
- Pathogenesis:
  - Can be 1° **cutaneous** disease (most commonly *A. flavus*) via direct inoculation (e.g., IV catheter, trauma sites, burn sites, and disturbed skin under dressings) vs 2° **cutaneous** disease (most commonly *A. fumigatus*; more common, typically in immunosuppressed, esp. neutropenic) via inhalation → pulmonary aspergillosis → disseminated disease
    - Both can → hematogenous spread with a tendency for **vascular invasion causing thrombus and necrosis**
- Clinical presentation: six clinical forms including erythematous edematous plaques, nodules with necrotic centers, hemorrhagic bullae, and necrotic ulcers
  - Can involve CNS, heart, kidneys, bone, and GI tract
- Treatment: azoles, echinocandins, and amphotericin B

## Fusarium

- Species: *Fusarium solani* most common
- Geography: ubiquitous in soil
- Microscopy: **45° angle branching**, similar to *Aspergillus*
- Pathogenesis: more common in immunosuppressed; severe burns (**most common fungus cultured in burn patients**); cutaneous disease via direct inoculation and hematogenous spread with a tendency for vascular invasion causing thrombus/necrosis
- Clinical presentation: erythematous; edematous plaques more common than subcutaneous nodules (purpuric or ecthyma gangrenosum-like); panniculitis
- Treatment: no well-established treatment due to drug resistance (cannot treat with caspofungin); localized disease amenable to surgical debridement and systemic antifungal therapy



**Figure 5-17.** Septated hyphae of *Aspergillus* spp. in the dermis (PAS stain, original magnification 40x). (From Galimberti R, Torre AC, Baztán MC, Rodríguez-Chiappetta F. Clinics in Dermatology. 30:6:633–650 Elsevier, 2012.)



**Figure 5-18.** Zygomycosis. Nonseptate thick hyphae (H&E, 40x). (Courtesy of Dr Liliana Salgado.)

### Penicilliosis

- Species: *Penicillium marneffei* is only pathogenic species
- Geography: Southeast Asia
- Microscopy: intracellular parasitic phase in macrophages
- Pathogenesis: acquired by inhalation or possibly abrasions; **bamboo rat exposure** may be risk factor
- Clinical presentation: similar to histoplasmosis: fever, weight loss, lymphadenopathy, cough, and hepatosplenomegaly
  - Cutaneous manifestations: papules with central necrosis and **molluscum-like lesions**; face, arms, and trunk are most common sites
- Treatment: polyenes (amphotericin B and terbinafine) and azole antifungals

## V. Uncommon fungal, protozoal and algae pathogens

### Zygomycosis (mucormycosis)

- Species:
  - Order *Mucorales*, genera *Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*, and others – **systemic and cutaneous** disease
  - Order *Entomophthorales* (e.g., *Conidiobolus coronatus*) – rare, chronic, **cutaneous, and subcutaneous** infection in tropics
- Geography: ubiquitous in soil and decaying vegetation
- Microscopy (Fig. 5-18): **broad ribbon-like nonseptate** hyphae with 90° angle branching, angioinvasive with thrombosis
- Pathogenesis: most commonly enter via respiratory tract (though there are other portals of entry like skin), and can **invade blood vessels → thrombosis/infarction/necrosis**
  - More common in immunosuppressed patients, but also nonimmunodeficient (e.g., severe diabetes and severe burns)

- Disease manifestation – subtypes include: **rhinocerebral** (most common subtype; usually in **diabetes** patients with DKA), pulmonary, gastrointestinal, **primary cutaneous** (from surgery, catheterization, or burns), and disseminated
  - All forms are rapidly progressing and **commonly fatal**
  - Cutaneous lesions (can be primary or secondary) typically indurated, **necrotic black plaques/eschars** most commonly seen on face (nasal and oral in rhinocerebral type)
  - Rhinocerebral type may have epistaxis, facial pain, periorbital cellulitis, proptosis, and loss of extraocular muscle movement (2° to cranial nerve palsies)
- Treatment: **aggressive surgical resection** of all necrotic areas (crucial to survival of patient) and **amphotericin B** (lipid formulation); posaconazole may be alternative

### Phaeohyphomycosis

- Due to **dematiaceous** (pigmented) fungi: *Exophiala jeanselmei* (#1 cause), *Wangiella dermatitidis*, *Alternaria*, *bipolaris*, *Phialophora*, and *Curvularia*
- Geography: tropics and temperate zones
- Microscopy: **cyst** composed of macrophages and short hyphae, with a fibrous capsule
  - **Hyphae are pigmented/brown**, and stain (+) with Fontana-Masson
- Pathogenesis: immunosuppressed patients
- Clinical presentation: **subcutaneous, possibly draining, inflammatory abscesses/cysts** (may mimic Baker cysts)
- Treatment: **excision** and itraconazole

### Protothecosis

- Species: *Prototheca wickerhamii*, not a fungus but an **algae**
- Geography and pathogenesis: introduced into skin via trauma in **contaminated water**
- Microscopy: organisms have a **morula-like appearance** on H&E
- Clinical presentation: nodules/ulcers/plaques and/or **olecranon bursitis**
- Treatment: excision and systemic antifungals (e.g., amphotericin B)

### Rhinosporidiosis

- Species: *Rhinosporidium seeberi*, not a fungus but a **protozoa**
- Geography: tropics (southern India and Sri Lanka)
- Pathogenesis: likely caused by **contaminated water** contact as this is a fish parasite
- Microscopy: **Very large** (up to 300 µm sporangia containing trophozoites in dermis)
- Clinical presentation: slow-growing **friable, red-purple, soft, lobulated, mucosal polyps**, particularly on **nose** (associated with epistaxis), and conjunctivae; young men most commonly
- Treatment: excision



## 5.5 PARASITES AND OTHER CREATURES

### Parasitic infestations

#### Scabies

- *Sarcoptes scabiei* var. *hominis*
- Most consistent factor associated with scabies is overcrowding
- Host-species restricted (each species lives only on its natural host)
- 30-day life-cycle within stratum corneum; 1 week survival off human; classically affects **interdigital webspaces**, wrists, **genitals** (a/w chronic, reactive inflammatory nodules), and trunk; **mineral oil scraping** demonstrates scabies mite
- Crusted (Norwegian) scabies in immunosuppressed patients
  - Most common complication is secondary bacterial infections
- Treatment of choice = **permethrin 5% cream**; other treatment options = ivermectin or lindane

#### Lice

- Head louse – *Pediculus humanus capitis*
  - Active infection only if within 5 mm from scalp; most commonly located in occipital and **postauricular** areas
  - Mites can survive 36 hours w/o blood meal; nits are **strongly adherent** to hair shaft and can survive 10 days w/o blood meal
- Body louse – *Pediculus humanus corporis*
  - Larger, but similar shape to head louse
  - Vector in **epidemic typhus** (*R. prowazekii*), **louse-borne relapsing fever** (*B. recurrentis*), and **trench fever** (*B. quintana*)
  - Live and lay eggs on clothing; more common in **homeless** population (since unable to change/wash clothes regularly)
- Pubic louse – *Phthirus pubis*
  - Identify by four frontal crab-like appendages and short/broad body
  - **Maculae ceruleae** (blue-gray macules due to bites) may be seen on surrounding skin
- Treatment – permethrin 1%, pyrethrins or malathion (**flammable**, only for age >2 years old)

#### Tungiasis (Fig. 5-19)

- Burrowing flea – *Tunga penetrans*
  - Female burrows head-first into skin (usually feet/toes) and extrudes eggs from punctum before dying and being sloughed with epidermis; can → gangrene
  - Most common: **Caribbean**, Central/South America, and sub-Saharan Africa
  - Treatment: surgical removal or ivermectin (should do tetanus prophylaxis)

#### Myiasis

- Infection with dipterous larvae
  - *Dermatobia hominis* (**human botfly**; most common)
    - Via exposed skin
    - Can be transmitted by mosquito
  - Tumbu (*Cordylobia anthropophaga*)
    - Larva are deposited on damp clothing and penetrate skin when clothes are worn
  - Wound myiasis (*Cochliomyia hominivorax*, *Chrysomya bezziana*) – larvae cannot penetrate intact skin; once laid within open wound, penetrate subcutaneous structures and can continue to penetrate through cartilage and bone (leading to cranial penetration if developing near nose)
- Treatment: removal of larvae + antibiotic for superinfection

#### Protozoa

#### Leishmaniasis

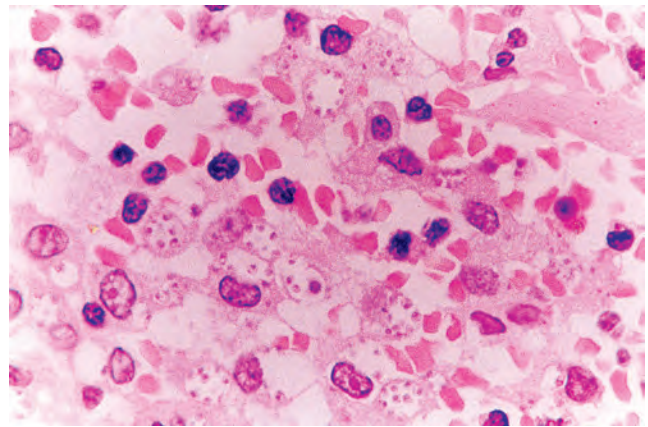
- Chronic infection due to **obligate intracellular protozoan**, *Leishmania* spp.
  - Exist in 2 forms: promastigote and amastigote
  - **Vector: Sandflies** (*Phlebotomus* or *Lutzomyia*)
  - Reservoirs: mainly canines and rodents
- Pathogenesis: Within gut of sandfly, organisms proliferate into flagellated promastigotes → migrate to sandfly proboscis → sandfly bites human and transfers promastigotes → histiocytes engulf promastigotes, which then transform into amastigotes and multiply → develop clinical manifestations within weeks (cutaneous leishmaniasis) or many months-years later (mucocutaneous and visceral leishmaniasis)
- Leishmaniasis may classified by geographic region (Old world vs. New world), or clinical presentation (cutaneous, diffuse cutaneous, mucocutaneous, or visceral)
- Geographic classification:
  - Old world



**Figure 5-19.** Tungiasis – massive infestation of hand and feet in a cattle handler. (Courtesy of Dermatology Service, Santa Casa de Misericórdia, Porto Alegre, Brazil).



**Figure 5-20.** Smooth nodular cutaneous leishmaniasis lesions. (From Bailey MS, Lockwood DNJ. Clinics in Dermatology 25:2:203–211 Elsevier, 2012.)



**Figure 5-21.** Leishmaniasis. H&E section of skin with several Leishmania organisms inside histiocytes. (From Tyring SK, et al. Tropical Dermatology 1st edn. Elsevier, 2005.)

- *L. major*, *L. tropica* > *L. aethiopica*, *L. infantum*, and others
- Vector: *Phlebotomus* sand flies
- **New world**
  - *L. mexicana*, *L. braziliensis*, *L. amazonensis*, and others
  - Vector: *Lutzomyia* sand flies
    - ◆ Also the vector of *B. bacilliformis* (→ verruga peruana, Carrion disease, bartonellosis, Oroya fever)
- Clinical classification (4 major forms):
  - **Cutaneous**: restricted to skin; more common in Old World (90% occur in Middle East, Brazil and Peru; Texas is the only endemic area in USA)
    - Old world cutaneous
      - ◆ Most common agents: *L. major*, *L. tropica* (>*L. infantum*)
      - ◆ Begins as a **solitary**, small, erythematous edematous nodule at bite site (usually **exposed skin sites**—arms, face, legs) that ulcerates or becomes verrucous (Fig. 5-20) → may later develop **sporotrichoid spread** with satellite lymphatic nodules and lymphangitis → heals with **scarring** over months to years
    - New world cutaneous
      - ◆ Most common agents: *L. mexicana* (>*L. braziliensis*)
      - ◆ More varied presentation: ulcerations (**Chiclero ulcer** = ear lesion in workers who harvest chicle gum in forest), impetigo-like, lichenoid, sarcoid-like, nodular, vegetating, and miliary
  - **Diffuse Cutaneous**: more widespread cutaneous lesions; usually arises in immunosuppressed pts
    - Most common agent: *L. amazonensis* (Americas), *L. aethiopica* (Africa)
    - Multiple keloidal lesions of face (esp. nose) and extremities
  - **Mucocutaneous**: affects skin and mucous membranes; almost always in New World
- Predominantly New world subspecies: *L. braziliensis* (> *L. amazonensis*, *L. panamensis*, and *L. guyanensis*)
- Present with lip, nose and oropharyngeal infiltration and ulceration
- Progressive nasopharyngeal destruction → airway obstruction, mutilation of mouth and **perforation of nasal septum** (aka “tapir face” or espundia)
- **Visceral (Kala-azar, “black fever”)**: most severe form; due to systemic infection of bone marrow liver, spleen; Old World > New World; long incubation time months-years
  - Most common agents: *L. donovani* (India, Sudan, Bangladesh; most common cause in adults), *L. infantum* (Europe; often a/w HIV), *L. chagasi*
  - Present with fever, weight loss, diarrhea, abdominal tenderness, lymphadenopathy, hepatosplenomegaly, nephritis, intestinal hemorrhage, and **death within 2 years** (if not treated)
  - Skin changes:
    - ◆ Specific: papules, ulcers at bite site
    - ◆ Non-specific: purpura, **hyperpigmentation** (hence the name “black fever”), kwashiorkor changes (brittle hair)
  - **Post-kala-azar dermal leishmaniasis**: new-onset cutaneous leishmaniasis lesions that arise up to 20 years after presumed recovery from untreated visceral leishmaniasis
- Diagnosis
  - PCR is most sensitive and specific test
  - Culture: **Novy-McNeal-Nicolle medium**
  - Histology: amastigotes with **kinetoplasts** are arrayed around periphery of parasitized histiocyte cytoplasm (“**Marquee sign**”) (Fig. 5-21); organisms are best seen on **Giemsa**
  - Montenegro delayed-skin reaction test is positive in majority of cutaneous leishmaniasis; remains positive after cure and is negative in febrile phase of visceral leishmaniasis
- Prognosis: most cases of Old World CL self-resolve within 15 months; New World CL due to *L. Mexicana*

self-resolves in 75%; mucocutaneous leishmaniasis (*L. braziliensis* and *L. panamensis*) does NOT self-resolve and requires treatment to prevent progressive destruction

- Treatment: treat if severe/widespread, mucocutaneous, and/or to decrease scarring
  - Cutaneous and mucocutaneous leishmaniasis: pentavalent antimony (ToC)
  - Visceral leishmaniasis: Amphotericin B (ToC)

## Trypanosomiasis

- African trypanosomiasis (sleeping sickness)
  - Species: *T. brucei gambiense* (West Africa)/*T. brucei rhodesiense* (East Africa)
  - Vector: Tsetse fly (*Glossina*)
  - Clinical presentation:
    - Trypanosomal chancre (earliest sign: local pruritic inflammatory reaction at site of inoculation [48 hours]) → local lymphadenopathy and ulcerates → eschar
    - Fever, headache, and joint pain at irregular intervals
    - Winterbottom's sign (posterior cervical LAD) (2 to 3 weeks) → trypanids (erythematous, urticarial or macular diffuse eruptions [6 to 8 weeks]) → neurologic changes and Kerandel's deep delayed hyperesthesia, daytime sleepiness (late stage)
  - Disease course: progressive over weeks to months (East Africa), months to years (West Africa)
  - Treatment: suramin or pentamidine (early), melarsoprol, or eflornithine (CNS involvement)
- American trypanosomiasis (Chagas disease)
  - Species: *T. cruzi*
  - Vector: triatomine bug (*Reduviidae*)
    - Central/South America
  - Clinical presentation: local inflammatory lesion (often on face) at site of entry (Chagoma) → Romanña's sign (Fig. 5-22) (unilateral eyelid edema and conjunctivitis at site of inoculation) → rapid



**Figure 5-22.** Romanña sign. Acute Chagas disease in a young girl with Romanña sign present in the left eye. (From Lupi O. et al. Tropical dermatology: Tropical diseases caused by protozoa. J Amer Acad Dermatol 2009;60:6:897–925.)

unilateral painless bipalpebral edema → late heart, esophagus, and intestinal enlargement (megacolon)

- Treatment: benznidazole and nifurtimox

## Toxoplasmosis

- Species: *Toxoplasma gondii*
- Geography: worldwide
- Vector: intestinal parasite of cats, but also infects dogs and rabbits
- Clinical presentation: hemorrhagic or necrotic papules
  - Acquired cutaneous disease occurs in pregnant women and immunocompromised patients
  - Congenital disease (TORCH syndrome) – see Pediatric Dermatology
- Treatment: sulfadiazine and pyrimethamine

## Helminths

### Cutaneous larva migrans

- Most common tropical parasite dermatosis; found in animal feces
- Species – *Ancylostoma brasiliense* (most common); also *A. caninum*
- Clinical presentation: erythematous serpiginous cutaneous eruption (usually on feet) as a result of larva penetrating intact epidermis, but unable to penetrate human basement membrane zone (therefore unable to cause systemic disease)
  - Moves 2–10 mm/hr
- Treatment: albendazole, ivermectin, topical/oral thiabendazole, and liquid nitrogen

### Larva currens

- Moves faster (5–10 cm/hr)
- *Strongyloides stercoralis*
- Often indurated serpiginous papule on buttocks/groin
- If disseminated, may get periumbilical (thumbprint) purpura and petechiae on trunk/proximal extremities
  - Loeffler's syndrome = chronic strongyloidiasis (affects lungs and GI tract; eosinophilia)
- Caused by contact with contaminated soil (e.g., sitting on beach)
- ELISA can help with diagnosis
- Treatment: ivermectin or thiabendazole

### Onchocerciasis (“River blindness”)

- Species: *Onchocerca volvulus*
- Vector: Simulium fly (black fly; also vector for tularemia; has also been implicated in Fogo selvagem form of pemphigus; present near fast-flowing rivers)
  - Geography: sub-Saharan Africa, South America, and Yemen
- Pathogenesis: nodules of female microfilariae; male microfilariae migrate between nodules to mate
- Clinical presentation: pruritic papules (can be acute, chronic, or lichenified) → leopard skin (depigmentation and atrophy); nodules (onchocercomas) over bony



prominences; may develop **Mazzotti reaction** if given **diethylcarbamazine**

- Can → **blindness**
- Treatment: **ivermectin (treatment of choice)**; newer trials with doxycycline (kills symbiotic *Wolbachia* bacteria); **surgical excision of onchocercomas**

## Loiasis

- Species: *Loa loa*
- Vector: *Chrysops* (Mango/deer flies; also transmit tularemia)
  - Geography: West and Central Africa
- Clinical presentation: **calabar swellings** (recurrent migratory focal angioedema on limbs); **visible migration of adult worm across eyes**
- Treatment: **diethylcarbamazine**

## Filariasis

- Species: *Brugia malayi/timori* and *Wuchereria bancrofti*
- Vectors: multiple mosquito spp. of *Culex* (also West Nile virus vector), *Aedes* (also vector of chikungunya fever, Dengue fever, and yellow fever), and *Anopheles* (also vector of malaria and yellow fever) mosquitoes
- Clinical presentation:
  - Acute – lymphangitis
  - Chronic – granulomatous reaction in lymphatics → **lymphedema**
- Treatment: Diethylcarbamazine (ToC)

## Swimmer's itch and Seabather's eruption

- Swimmer's itch ("cercarial dermatitis")
  - Species: *Schistosoma*, during the cercarial stage (snails are a vector)
    - Northern United States and Canada **fresh water**
  - Clinical presentation: papules and papulovesicles on **uncovered skin** 10 to 15 hours post exposure, lasts 5 to 7 days
- Seabather's eruption (NOT a helminthic infection)
  - Species: *Edwardsiella lineata* (sea anemone) and *Linuche unguiculata* (thimble jellyfish) during larval stage
    - Southern United States and Caribbean **salt water**
  - Clinical presentation: pruritic papules and wheals in **covered areas** within hours with new lesions for days (Fig. 5-23)

## Trichinosis

- Species: *Trichinella spiralis*
- Geography: worldwide with domestic and sylvatic infection cycles
  - Most common reports are rural Asia and Latin America
- Vectors:
  - Domestic cycle – **pigs**, which are then **eaten undercooked** (eating undercooked bears = less common cause)

- Sylvatic cycle – scavengers and carnivorous animals (wild canines and felines, birds, raccoons, boars, and walruses) eat infected rodents, and are themselves eaten undercooked by humans
- Pathogenesis: humans eat animal meat (muscle) that contains larval cysts → these encyst in GI tract and mature into adults → reproduction occurs and larvae are produced, which leaves the GI tract and encyst in skeletal muscle
- Clinical presentation:
  - Primary dermatologic manifestation is **periorbital edema** (as a result of type I allergic reaction) and petechiae during parasite migration (esp. **splinter hemorrhages**)
- Diagnosis: peripheral eosinophilia and IgE are clues; **muscle biopsy is diagnostic**
  - ↑IgE may persist years after disease resolution
- Treatment: mebendazole or albendazole; may use systemic steroids for moderate to severe hypersensitivity reactions

## Dracunculiasis (Guinea worm)

- Species: *Dracunculus medinensis*
- Vector: *Cyclops* water flea at copepod stage
- Clinical presentation: **nodules and ulcers on lower extremity** (after ingestion of infected Cyclops, the organism travels from intestines to subcutaneous tissue, where adult worms emerge from lesion when reexposed to water)
- Prevention: drinking filtrated/boiled water prevents ingestion of copepods that contain larva
- Treatment: **removal of worm** (ToC), wound care, and metronidazole



**Figure 5-23.** Classic lesions of seabather's eruption in covered areas. The disease is caused by larvae of *Linuche unguiculata*. (Photograph of the planula courtesy of Lang da Silveira. Photograph of the lesions courtesy of Vidal Haddad Jr, MD, PhD, São Paulo, Brazil.)





**Figure 5-24.** *Cimex* spp. The bites from bedbugs are not accompanied by severe manifestations in nonsensitized persons, but they can cause notable erythema, edema, and itching in those persons allergic to the bites (especially atopic individuals). (From Haddad V. Tropical dermatology: Venomous arthropods and human skin. J Amer Acad Dermatol 2012;67:3:e1–e14.)

## Cutaneous amebiasis

### Free-living amoeba

- *Acanthamoeba* – subacute granulomatous amebic encephalitis; skin lesions → **chronic ulcers**
- *Balamuthia* – painless, red, and granulomatous plaque on **central face** > trunk/extremities, which precedes CNS involvement
- *Naegleria* – fulminate, **fatal** acute necrotizing meningoencephalitis

### GI-associated amoeba

- *Entamoeba histolytica*
  - Usually associated with **amebic colitis** and/or liver/lung involvement
  - Cutaneous lesions may spread to **perianal region** from GI involvement, or be **sexually transmitted** with a painful ulcerating erythematous plaque near the site of inoculation

## Bites and stings

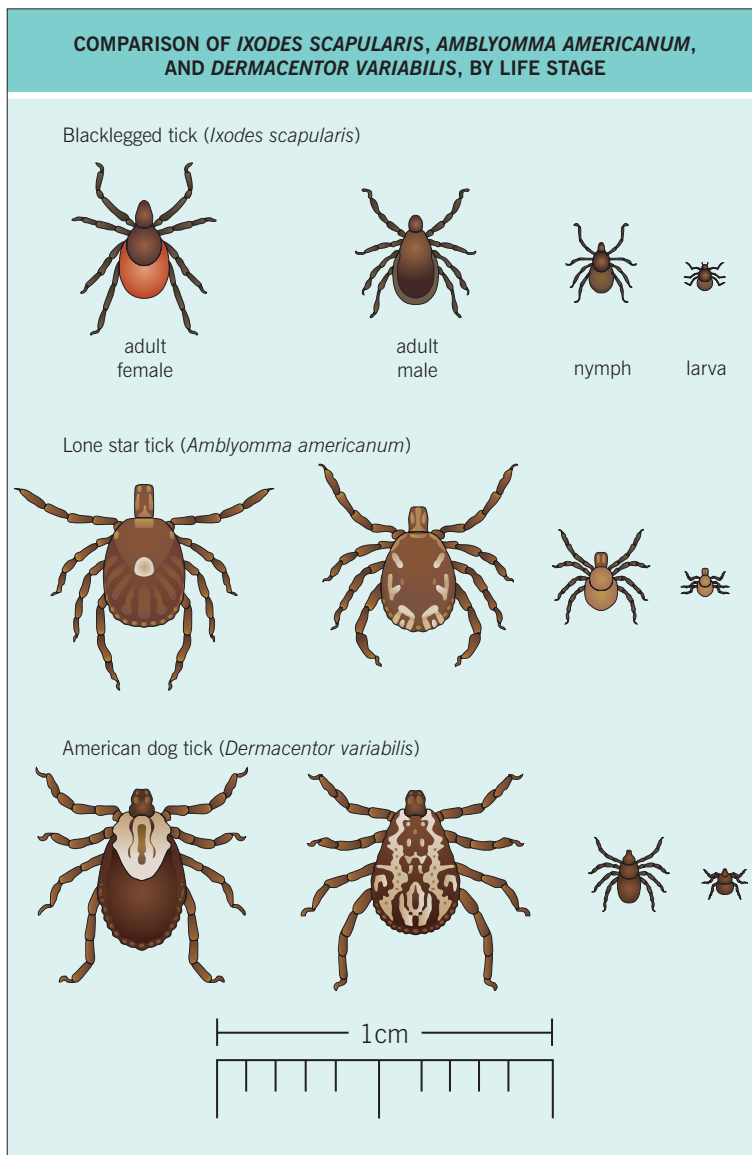
### Biting and stinging insects

- Immediate reactions are as a result of histamine, serotonin, formic acid, or kinin release
  - 1/4 of cases of **anaphylaxis** are as a result of stings from insects (order **Hymenoptera**)
  - Bullous insect bites – several cm tense bullae without significant edematous/erythematous bases
- **Fire ants** (*Solenopsis*): bites → 5 mm to 1 cm sterile pustules on lower extremities
  - Toxin = **solenopsin D** (piperidine alkaloid)
- **Bees/wasps/hornets** (*Hymenoptera*): toxin = **phospholipase A**; can → anaphylaxis

- **Bed bugs**
  - Species: *Cimex lectularius* (Fig. 5-24)
  - Nitrophorin is one of its salivary products responsible for human immune reaction; p/w grouped “**breakfast, lunch and dinner**” urticarial papules at bite sites
- *Lytta vesicatoria*/Spanish fly (blister beetles)
  - **Cantharidin** derived from heme-lymph discharge; p/w blisters at sites of contact
- **Fleas**
  - Rat flea (*Xenopsylla cheopis*) is vector for *R. typhi* → **endemic typhus** and *Y. pestis* → **bubonic plague** (treatment: streptomycin and gentamicin)
  - Cat flea (*Ctenocephalides felis* and *canis*) is vector for *Bartonella henselae* (→ cat scratch disease, bacillary angiomatosis), AND *Bartonella Quintana* (→ bacillary angiomatosis)
  - *Pulex irritans* is the human flea; also affects dogs
- **Lepidopterism** (caterpillar dermatitis)
  - Direct contact with hairs and toxin-mediated reactions (not allergy)
  - **Train-track appearance of urticaria or hemorrhage**
  - Ophthalmia nodosa are ocular reactions as hairs tend to migrate inward
  - Specific types of caterpillars:
    - Puss (*Megalopyge opercularis*): lightly brown and wooly appearance; results in painful, **linear petechiae**
    - Io (*Automeris io*): green with longitudinal white strip
    - Gypsy (*Lymantria dispar*): histamine in hair, which can become airborne
    - Saddleback (*Sibine stimulea*): green saddle-like area on back
- DEET (N,N-diethyl-3-methylbenzamide) is overall the most effective insect repellent

## Arachnids (ticks, mites, spiders, and scorpions)

- **Ticks** (Fig. 5-25)
  - *Ornithodoros*
    - Soft-bodied tick
    - Identification: warty/rough, gray, and soft appearance
    - Transmits *B. duttonii* (tick-borne relapsing fever)
  - *Dermacentor*
    - Identification: alternating light and dark bands on body with brown legs
    - Transmits RMSF (#1 cause), **tularemia**, tick paralysis, and **human granulocytic anaplasmosis/ehrlichiosis**
  - *Ixodes pacificus*, *ricinus*, *scapularis*, and *dammini*
    - Identification: dark legs and solid-colored body with darker scutula
    - Transmits **Lyme disease** (#1 cause; *B. burgdorferi*), **acrodermatitis chronica atrophicans** (*B. garinii* and *B. afzelii*), **babesiosis** (#1 cause), and **human granulocytic anaplasmosis**
  - *Amblyomma* – lone star tick
    - Identification: white dot on back (female)



**Figure 5-25.** Comparison of *Ixodes scapularis* (blacklegged tick), *Amblyomma americanum* (lone star tick), and *Dermacentor variabilis* (American dog tick) by life stage. (From Chapman AS, et al. MMWR Recomm Rep. 2006;55:1–27. Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

- Transmits human monocytic ehrlichiosis; tularemia; African tick bite fever; Brazil spotted fever
- **Mites**
  - *Demodex* (*Demodicidae*)
    - Live in hair follicles of humans
    - Possible association with rosacea/perioral dermatitis
  - Free-living mites
    - Chigger/harvest mite (*Trombicula alfreddugesi*)
      - ◆ Vector for *R. tsutsugamushi*, which → scrub typhus
      - ◆ Causes grouped pruritic papules on lower extremities/ankles and waistband
      - ◆ Causes summer **penile syndrome** in boys
    - House mouse mite (*Allodermanyssus sanguineus*)
      - Vector for *R. akari* → rickettsialpox
    - Dust mite (*Dermatophagoides*)
      - Involved in indoor allergies in atopic patients
  - Fowl mite (*Dermanyssus* and *Ornithonyssus*)
    - Vector for western equine encephalitis
  - Walking dandruff (*Cheyletiella*)
    - Caused by contact with dogs/cats – asymptomatic in dogs/cats but itchy eruption in human
  - Grain mite (*Acarus siro*)
    - Agent of Baker's itch
  - Cheese mite (*Glyciphagus*)
    - Agent of Grocer's itch
- **Spiders**
  - *Latrodectus mactans* – **black widow** spider; has characteristic **red hourglass** on body
    - Acute pain and edema at site
    - Systemic symptoms: chills, **abdominal pain/rigidity**, rhabdomyolysis, chest pain, sweating, hypertension, and shock
    - **α-Lactotoxin** depolarizes neurons
    - Treatment: IV calcium gluconate; antivenom; **benzodiazepine** supportive



**Figure 5-26.** *Loxosceles reclusa* (brown recluse spider). A characteristic “violin” or “fiddle” marking appears on the head and thorax. (Courtesy of Dr. Robert G. Breene, American Tarantula Society, South Padre Island, Texas.)

- *Loxosceles reclusa* – **brown recluse** (Fig. 5-26) spider; characteristic dark brown-black violin/fiddle shaped marking
  - Necrosis with eschar formation at site of bite (which is painless; erythema → ischemia → thrombosis)
  - Toxins: sphingomyelinase D and hyaluronidase (allows eschars to spread)
  - Can have hemolytic anemia, shock, and death
  - Treatment: do not debride; supportive; antivenom
- *Phidippus formosus* – jumping spider
  - Dark and hairy with four eyes (two larger centrally and two smaller ones laterally)
  - Toxin: hyaluronidase
  - Is aggressive and bites, but no systemic symptoms
- *Lycosidae* – wolf spider
  - Large brown spider with black patterns and eight eyes
  - Toxin: histamine
- *Chiracanthium* – sac spider
  - Yellow-colored
  - Toxin: lipase
- *Tegenaria agrestis* – hobo spider
  - Herringbone pattern on abdomen
  - Painless bite → local necrosis/eschar
  - Web is funnel-shaped
- *Peucetia viridans* – green lynx spider; has unique neon green color with red spots
  - Green colored with red spots
  - Painful bite without systemic symptoms
- *Theraphosidae* – tarantula
  - Urticating hairs ejected when threatened; can → ophthalmia nodosa (chronic granulomatous reaction in eyes; may result in blindness)
- **Scorpions** (*Centruroides sculpturatus* and *gertschi*)
  - Pain and paresthesia out of proportion to skin lesions
  - Systemic symptoms: convulsions, hemiplegia, temperature instability, tremor, arrhythmia, pulmonary edema, and hypertension



**Figure 5-27.** Linear plaques, erythema, and edema in a girl following contact with the tentacles of a Portuguese man-of-war. (Courtesy of Dr. Vidal Haddad Junior)

## Millipedes and centipedes

- Centipedes (*Chilopoda* class; *Scolopendra* spp)
  - One pair of legs per segment
  - Bites produce pain and paresthesia
    - Two puncture wounds
- Millipedes (*Diplopoda*)
  - Two pairs of legs per segment
  - Chemical irritant contact dermatitis from secretions → burn and blistering

## Snake bites

- *Viperidae/Crotalidae* (copperhead and rattlesnake):
  - **triangular head** with deep nostril pits
  - Multiple toxins, including thrombin-like glycoproteins
  - **Thrombocytopenia and DIC**
- *Elapidae* (coral snake) round eyes, characteristic **red, yellow and black** banding (mnemonic: “red on yellow kills a fellow”)
  - $\alpha$ -Neurotoxin – causes neurologic symptoms, nausea, headache, abdominal pain, and paresthesia
  - Phospholipase A2 causes wound effects

## Marine injuries

- Cnidarians (jellyfish, Portuguese man of war, coral, and anemones)
  - Produces specialized cells – nematocysts
  - **Flagellate eruption in affected areas** (Fig. 5-27)
  - Physical or osmotic trigger releases a coiled filament that discharges toxins
    - **Vinegar (dilute acetic acid)** denatures nematocysts in some, but not all species

- *Chironex fleckeri* (Pacific box jellyfish) stings can → shock and associated fatality
- Portuguese man of war (*Pysalia* spp.) contain a heat-labile toxin that produces cardiac disturbances and paralysis
  - Skin lesions are hemorrhagic and vesicular
- **Echinoderms**
  - Sea urchins have fragile spines that break off in wounds → foreign body reaction
  - Sea cucumbers eject an irritating liquid (holothurin) → conjunctivitis

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# Neoplastic Dermatology

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## NEOPLASTIC DERMATOLOGY

- General features of a benign neoplasm:
  - Clinically: well-demarcated, uniform color, unchanged for years, and lack of concerning symptoms (bleeding, ulceration, and pain)
  - Histologically: **well-circumscribed, bland cytology**; lacks all of the following: architectural disorder, necrosis, cytologic atypia, and atypical mitotic figures
- General features of a malignant neoplasm:
  - Clinically: rapid growth or new onset lesion with concerning features, such as pigment variegation, ulceration, pain, and bleeding
  - Histologically: poorly circumscribed proliferation of cells with **atypical cytology** (nuclear pleomorphism, hyperchromatic cells, ↑N:C ratio, prominent nucleoli, and abnormally shaped nuclei); **architectural disorder** (infiltrative, destroys neighboring structures, and perineural/intravascular invasion); **signs of hyper-proliferative state** (↑mitotic figures for given tissue type and tumor necrosis), **atypical mitoses** (do not resemble any normal phase of cell division)

## 6.1 KERATINOCYTIC NEOPLASMS

### Seborrheic keratosis

- Very common, benign; onset fourth decade
- Familial disposition, autosomal dominant (AD) inheritance w/ incomplete penetrance
- Associated with (a/w) **sun-exposure** (↓incidence on “double-clothed areas” such as buttocks and genitalia), *FGFR3* and *PIK3CA* activating mutations
- Well-demarcated, waxy/verruccous **brown “stuck-on” papules** on hair-bearing skin; spares mucosal sites
- Histology: acanthosis, papillomatosis, hyperkeratosis with **pseudohorn cysts**, **flat base (“string sign”)**, bland keratinocytes without atypia, or many mitotic figures (if present will be mild and associated with irritation/inflammation) (Table 6-1)
- **Sign of Leser-Trelat**: widespread eruption of SKs on trunk; a/w underlying adenocarcinoma (GI #1)
- Multiple variants (Table 6-2)

### Porokeratosis

- Subtypes
  - **Porokeratosis of Mibelli**: onset in infancy or childhood; **extremities**; large (often >3 cm) **circinate plaque** with keratotic border
  - **Disseminated superficial actinic porokeratosis (DSAP)**: onset in middle age, F > M; numerous brownish-red macules w/ keratotic borders in sun exposed areas; most common on legs (rare on face); immunosuppression is risk factor
  - **Linear porokeratosis**: onset in newborns; linear lesion on extremities, follows lines of Blaschko (Fig. 6-1); highest risk of progression to SCC
  - **Punctate porokeratosis**: onset in adolescence; 1- to 2-mm “seed-like” papules on palms/soles

- Porokeratosis palmaris, plantaris, et disseminata (PPPD): onset in childhood/adolescence; occurs on palms/soles initially
- Porokeratotic eccrine ostial and dermal duct nevus: clinically resembles a nevus comedonicus of palm or sole (Fig. 6-2), but histology shows abundant **cornoid lamellae arising from acrosyringium**
- Histology: **cornoid lamella** (angled column of parakeratosis w/ underlying hypogranulosis and dyskeratotic cells); centrally between two cornoid lamellae the epidermis may be atrophic, hyperplastic, normal, or BLK-like
- SCC can develop in any subtype except **punctate form (0% risk)**; second lowest risk in DSAP; highest risk in linear form

## Epidermal nevus

- Hamartoma of epidermis and papillary dermis; onset in first year of life

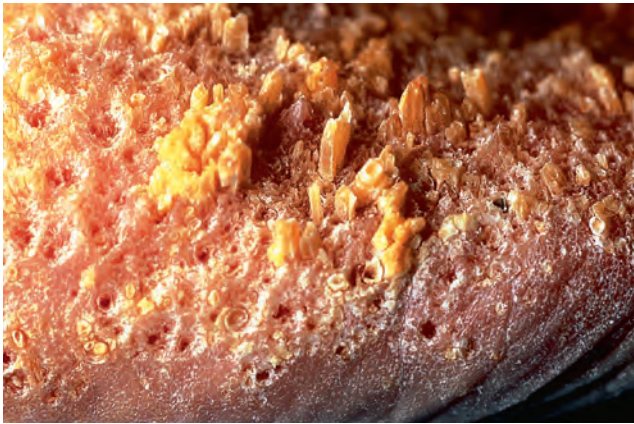
- Papillomatous, pigmented, linear plaques along Blaschko's lines
- Variants:
  - **Nevus unius lateris**: extensive unilateral plaques on trunk
  - **Ichthyosis hystrix**: extensive bilateral lesions on trunk
  - Inflammatory linear verrucous epidermal nevus (ILVEN): along lines of Blaschko without associated neurologic defects
  - **Epidermal nevus syndrome (Schimmelpenning syndrome)**: a/w developmental abnormalities (neurologic and musculoskeletal most commonly)
- Histology: epidermal papillomatosis; orthohyperkeratosis
  - May see **epidermolytic hyperkeratosis** as a result of genetic mosaicism (**defects in keratins 1 and 10**) → **↑risk bullous congenital ichthyosiform erythroderma in offspring**
- Mutations in **FGFR3** and **PIK3CA** have also been identified

Table 6-1. Seborrheic Keratosis Histologic Variants	
Acanthotic	<b>Most common type</b> ; presents as a dome-shaped papule; mostly acanthotic with less papillomatosis/hyperkeratosis; small basaloid keratinocytes with increased melanin, prominent horn pseudocysts
Hyperkeratotic	Prominent hyperkeratosis/papillomatosis (" <b>church spires</b> ") w/ less acanthosis/pseudocysts/pigmentation
Reticulated	<b>Thin interlacing strands</b> of basaloid cells, often pigmented, with horn pseudocysts, +/- lentigo at edges (these may evolve from lentigo)
Irritated	Less sharply demarcated base with lymphoid infiltrate; whorls of pink keratinocytes (" <b>eddies</b> ")
Clonal	Well-defined nests of paler/monotonous cells (Borst-Jadassohn phenomenon) <b>mimicking Bowen's disease</b> , melanoma, or hidroacanthoma simplex
Melanoacanthoma	Heavy pigment mostly in <b>dendritic melanocytes</b> (>keratinocytes)

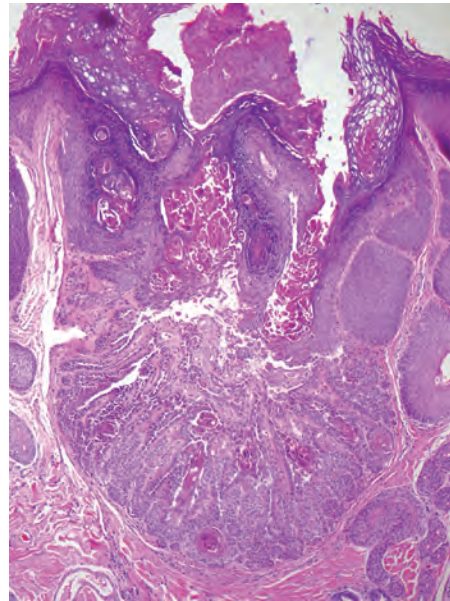


**Figure 6-1.** Porokeratosis. Several streaks of linear porokeratosis on the lower extremity. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

Table 6-2. Seborrheic Keratosis Variants and Other Benign Keratoses	
Dermatosis papulosa nigra	Darkly pigmented individuals, often <b>African Americans</b> ; onset in young adulthood, F > M; familial tendency; hyperpigmented keratotic papules on face; histology identical to SK, except horn pseudocysts are not common
Stucco keratosis	White scaly variant of SK; onset after 40 years old; M > F (4:1); white to gray hyperkeratotic papules/plaques symmetrically distributed on <b>lower legs</b> , feet; a/w <b>HPV-23b</b> , HPV-9, HPV-16, and HPV-37
Lichenoid keratosis	Often represents an <b>inflamed/regressing lentigo/SK</b> ; clinically <b>mimics BCC</b> or SCCIS; solitary pink/brown scaly papule trunk or forearms; fourth to seventh decade; F > M; histologically resembles lichen planus (but may have parakeratosis), often adjacent lentigo or SK
Inverted follicular keratosis	<b>Endophytic</b> variant of irritated seborrheic keratosis; white-pink firm solitary papules face/neck (especially <b>cheek and upper lip</b> ); middle aged/older adults; histology: endophytic SK with <b>prominent squamous eddies</b>
Large cell acanthoma	Likely represents an early macular SK/solar lentigo, flesh-colored to brown patch/plaque on sun exposed areas in older individuals; histology: papillomatosis, hyperkeratosis, elongation of epidermal rete with <b>large</b> , and <b>slightly atypical keratinocytes</b> +/- basal pigmentation
Acrokeratosis verruciformis of Hopf	Tan-flesh colored warty papules on <b>dorsal hands/feet</b> ; <b>AD</b> disorder of keratinization often <b>a/w Darier disease</b> ; <b>ATP2A2 mutations</b> ; histology: " <b>church spire</b> " hyperkeratosis and papillomatosis (identical to stucco keratosis)
Clear cell acanthoma (Degos's acanthoma)	Solitary erythematous papule on <b>lower leg</b> with 'wafer-like scale' at the periphery; histology: sharply demarcated zone of <b>pale keratinocytes (PAS+)</b> ; as a result of <b>phosphorylase deficiency</b> → <b>glycogen accumulation</b> ), <b>psoriasiform hyperplasia</b> , parakeratosis, loss of granular layer, and intraepithelial neutrophils <b>Mnemonic</b> : "looks like a well-demarcated papule of psoriasis comprised of clear keratinocytes"



**Figure 6-2.** Porokeratotic eccrine ostial and dermal duct nevus. Markedly hyperkeratotic spines arise from dilated eccrine ostia, corresponding to the histologic findings of coronoid lamellae. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



**Figure 6-3.** Warty dyskeratoma. The outward growth is verrucoid. The inward-growing component shows suprabasal acantholysis. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

### Nevus comedonicus

- Hamartoma; onset in childhood; worsens during puberty
- Comedones in a **linear array on face** > trunk
- **FGFR2 mutations** involved
  - **FGFR2** also involved in Alagille syndrome, Apert syndrome, cardiocranial syndrome, and Crouzon syndrome
- Histology: dilated epidermal invaginations filled w/ cornified debris

### Flegel disease (hyperkeratosis lenticularis perstans)

- Rare disorder with AD inheritance; adult-onset
- **Absent/altered lamellar granules (Odland bodies)** on electron microscopy
- **Disc-shaped** keratotic papules in symmetric distribution; **distal extremities** including palms/soles
- Histology: discrete orthohyperkeratosis overlying atrophic epidermis; lichenoid dermal inflammation

### Warty dyskeratoma

- Onset in fifth to seventh decade; M > F
- Solitary verrucous papulonodule w/ central keratotic plug usually on **head/neck**
- Histology: **cup-like epidermal invagination** with **acantholytic dyskeratosis** and corp ronds/grains (Fig. 6-3)
  - “Cup-shape” and solitary nature distinguishes from Darier’s

### Premalignant/malignant

#### Actinic keratosis

- Scaly, red plaques on sun-exposed areas; a/w chronic sun-exposure, male gender, older age, and fair skin phenotypes

- **UVB** responsible for AK development → induces **thymidine dimers** (C→T or CC→TT)
  - **p53 mutations** within keratinocytes → impaired apoptosis
- Histology: basal layer atypia (lower 1/3 epidermis) with budding/finger-like projections into dermis; “**Flag sign**”: overlying parakeratosis (pink) alternating with orthohyperkeratosis (blue); atypia and parakeratosis often spares follicles; solar elastosis in dermis
- Treatment: destructive measures (cryotherapy, ED&C, CO<sub>2</sub> ablation, topical 5-FU, imiquimod, PDT, ingenol mebutate, topical diclofenac, and TCA peel)
- Rate of transformation to SCC = 0.075%–0.096% per year

### Bowen’s disease (Squamous cell carcinoma in situ)

- Can progress from actinic keratosis or occur de novo
- Risk factors: elderly, chronic sun exposure, lightly pigmented skin, immunosuppression, arsenic exposure, ionizing radiation, HPV, and chronic irritation
- Hyperkeratotic erythematous patch or plaque; may affect any site
- Histology: acanthosis with **full-thickness keratinocytic atypia**, disorganized (“windblown”) architecture, ↑mitoses, dyskeratotic keratinocytes, and parakeratosis
- Variants: pigmented, pagetoid, verrucous, **Bowenoid papulosis** (multiple hyperpigmented penile papules, rarely progresses to invasive SCC), and **erythroplasia of Queyrat** (juicy red, erosive plaques on glans penis; more often progresses to invasive SCC)
- Treatment: excision, Mohs, and destructive therapies



## Invasive squamous cell carcinoma

- Erythematous scaly papulonodule/plaque; most commonly on **head/neck** and **dorsal extremities**
- Risk factors: chronic sun-exposure, male gender, older age, fair skin phenotypes, genetic syndromes, immunosuppression, HPV, radiation, chronic nonhealing wound (Marjolin's ulcer), **hypertrophic LE/LP**, **arsenic exposure**, and **chronic LS&A (genital)**
- Histology: full-thickness keratinocytic atypia w/ dermal invasion; tumor often "paradoxically differentiated" (tumor cells are MORE eosinophilic/keratinizing than surrounding keratinocytes)
  - Variants: poorly differentiated, spindle cell, acantholytic, pseudoglandular, Bowenoid, and verrucous
- Treatment: WLE, Mohs, ED&C, and radiation
- ↑Risk of metastasis: immunosuppressed state, location on **lip/ear**, diameter >2 cm, Breslow depth >2 mm, arising in **burn/scar (Marjolin's ulcer)**, poorly differentiated, and acantholytic (debatable)
- **Additional boards fodder**
  - ↑risk of SCC: patients w/ **CLL**, tobacco users, **vemurafenib**, long-term **voriconazole** prophylaxis, RA patients on MTX and etanercept, and **organ transplant (65 times ↑risk)**
  - **Genetic syndromes associated with SCC:**
    - Oculocutaneous albinism
    - Xeroderma pigmentosum
    - Dystrophic epidermolysis bullosa
    - Epidermodysplasia verruciformis
    - Dyskeratosis congenita
    - Porokeratosis, linear type
    - Keratitis, ichthyosis, deafness (KID) syndrome
    - Rothmund-Thompson syndrome
    - Werner's syndrome
    - Chronic mucocutaneous candidiasis

## Verrucous carcinoma

- Low-grade, locally destructive SCC a/w **HPV-6 and HPV-11**
- Large exo-endophytic nodule; three clinical variants:
  - Epithelioma cuniculatum: slow-growing mass **plantar foot (Fig. 6-4)**
  - Buschke-Lowenstein tumor (giant condyloma): large cauliflower-like growth in **anogenital** region
  - Oral florid papillomatosis: widespread oral lesions
- Histology: **very well-differentiated** (minimal to no cytologic atypia); bulbous/**pushing border**, massive size and ↑depth of base = clues to malignancy

## Keratoacanthoma

- Variant of SCC with unique features: **initial rapid growth** over weeks→ **self-resolves/involutes** over months
  - **Subungual KAs** are the exception (do NOT involute)
- Clinical variants: solitary, multiple, giant, intraoral, subungual, and keratoacanthoma centrifugum marginatum (can reach several centimeters)



**Figure 6-4.** Verrucous carcinoma of the foot (epithelioma cuniculatum). Verrucous carcinomas often reach large sizes before diagnosis because they are often treated as warts. (From Fitzpatrick JE, Morelli JG. *Dermatology Secrets Plus* 4th edn. Elsevier, 2011.)

- KA syndromes:
  - **Ferguson-Smith:** AD inheritance, rapid onset of multiple KAs; onset **third decade**, sun-exposed areas, and **resolves** spontaneously
  - **Grzybowski:** sporadic; 1000s of milia-like KAs in **later adulthood**; can involve **airway**; a/w **scarring, ectropion**, and mask-like facies
    - Mnemonic: "Old (later onset) Grizzlies Growl (airway affected)"
- Other associations: **Muir-Torre syndrome** (classic KAs, or KAs w/ sebaceous differentiation), immunosuppression, and HPV
- Histology: **crateriform**, endophytic nodule w/ **well-differentiated** keratinocytes (lacks significant atypia), central keratin plug, and peripheral inflammation w/ eosinophils
- Treatment: excision or Mohs; may observe if certain involuting

## Basal cell carcinoma

- Onset typically sixth to seventh decade, but can occur earlier; slow/indolent local growth; locally destructive (esp. morpheaform, infiltrative, and micronodular subtypes)
- Due to UV exposure (intermittent and intense > chronic and cumulative)
- **PTCH (chromosome 9q) mutations (most common)** > p53 point mutations (second most common)
- Sun-exposed skin, rare on palms, soles, and mucous membranes
- Numerous clinicopathologic variants (see [Table 6-3](#))
- General histologic features: nests of basaloid, uniform cells w/ high N:C ratio, peripheral palisading, epidermal connection (at least focally), myxoid stroma, stromal-epithelial retraction, and mitotic/apoptotic activity
- Treatment: WLE, Mohs, ED&C, radiation, imiquimod, topical 5-FU, and vismodegib (inoperable or metastatic BCC)

**Table 6-3.** Basal Cell Carcinoma Variants

Nodular	Favors <b>head/neck</b> ; histology: large nests (centrally +/- necrosis, cystic spaces); centrally, cells lack organization, prominent peripheral palisading, and may be ulcerated
Superficial	Erythematous scaly patch, most common type in younger patients, <b>trunk and extremities</b> (>head/neck); histology: multiple buds from epidermis do not extend beyond papillary dermis
Morpheaform	Scar-like pink to white plaque; histology: small angulated nests and cords within a sclerotic stroma; retraction not prominent; may be more deeply invasive
Micronodular	Smaller nests than nodular type; micronodules are separated by normal intervening collagen, and does not form a circumscribed contour at the deep aspect
Fibroepithelioma of Pinkus	Pedunculated, "soft/fleshy" lesion on <b>lower back</b> ; histology: thin anastomosing strands form a network within pinker stroma; retraction and myxoid material are less prominent
Pigmented	Nodular pattern BCC with aggregates of melanin in the nests and dermal melanophages
Infundibulocystic (keratotic, follicular)	Well-circumscribed, comprised of basaloid and squamoid cells in anastomosing cords, w/ horn cysts → <b>resembles benign follicular tumors</b> (trichoepithelioma and basaloid follicular hamartoma)
Basosquamous	Ambiguous term w/ variable meanings; may refer to: 1) BCCs with "squamoid appearance" (pinker cells, more cytoplasm, and keratinization), 2) carcinomas with features indeterminate between BCC and SCC, or 3) collision lesions of BCC + SCC

**Box 6-1.** Mnemonic

Genetic syndromes a/w multiple BCCs: "Green Berets Rarely Buy eXtra Shoes ... but they get a lot of BCCs from being in the sun!"

- Gorlin's
- Bazex-Dupré-Christol
- Rombo
- Brooke-Spiegler
- Xeroderma pigmentosum
- Schöpf-Schulz-Passarge

- Essentially no metastatic potential (dependent on stroma for growth)
  - Basosquamous subtype may behave more like SCC → ↑metastatic potential

**6.2 CYSTS****Epidermoid cyst**

- Clinical features
  - Firm dermal nodule with central punctum; any site, but most commonly head/neck/upper trunk
- Pathogenesis/histopathologic features
  - Derived from follicular infundibular epithelium; may arise primarily, or secondary to follicle disruption/

traumatic implantation; lined by stratified squamous epithelium w/ **intact granular layer** and **no adnexal structures** in the wall (vs vellus hair cyst and dermoid cyst); **laminated/flaky keratin** centrally

- Comments
  - Multiple epidermoid cysts may be a/w **Gardner's syndrome** (often have pilomatricoma-like areas histologically)

**Trichilemmal (pilar) cyst**

- Firm dermal nodule; **90% on the scalp**; usually multiple (70%); subset **AD inheritance**
- Pathogenesis/histopathologic features: Derived from isthmic follicular epithelium; stratified squamous epithelium **lacking granular layer**; **dense pink homogenized keratin** with frequent calcification centrally

**Proliferating trichilemmal cyst/tumor**

- Clinical features
  - Slow-growing dermal nodule; **scalp (90%)**; usually **elderly women**
- Pathogenesis/histopathologic features
  - Resembles trichilemmal cyst but more **proliferative centrally** w/ areas of multicystic architecture; well-circumscribed at periphery; variable cytologic atypia and mitotic activity
- Comments
  - Mostly benign, but small percentage behave aggressively → complete removal recommended

**Dermoid cyst**

- Clinical features
  - **Infants**; occur **along embryonic fusion lines** (most commonly **lateral eyebrow**)
- Pathogenesis/histopathologic features
  - Derived from entrapment of epidermis during embryogenesis; lined by stratified squamous epithelium with **granular layer** and **adnexal structures (hair follicles and sebaceous glands) in cyst wall**
- Comments
  - Be careful if biopsy b/c may have intracranial connection

**Vellus hair cyst**

- Clinical features
  - Multiple ("eruptive") domed and flesh-colored or **hyperpigmented papules**; trunk; subset **AD inheritance**
- Pathogenesis/histopathologic features
  - Same histology as epidermoid cyst, but has **multiple vellus hairs** in cyst cavity

**Steatocystoma**

- Clinical features
  - Single or multiple (**multiplex – AD inheritance**) lesions; chest/axilla/groin; drain oily fluid if punctured

- Pathogenesis/histopathologic features
  - Lined by thin stratified squamous epithelium with no granular layer and **thin bright pink corrugated** (“shark-tooth”) cuticle; **sebaceous glands in wall**
- Comments
  - Multiplex form with **KRT17 mutations**; a/w **pachyonychia congenita type 2**

## Hidrocystoma

- Clinical features
  - Translucent **bluish cysts**; face
- Pathogenesis/histopathologic features
  - Unilocular or multilocular cyst with low cuboidal lining +/- decapitation secretion (if apocrine); lumen appears empty
- Comments
  - May be a/w **Schöpf-Schulz-Passarge** (multiple hidrocystomas, syringofibroadenomas, PPK, hypodontia, and hypotrichosis)

## Bronchogenic cyst

- Clinical features
  - Solitary; present at birth; **suprasternal notch**/anterior neck
- Pathogenesis/histopathologic features
  - Sequestration of respiratory epithelium during embryogenesis; pseudostratified, ciliated columnar cells with **goblet cells**; +/- **smooth muscle**/mucous glands/**cartilage** in wall
- Comments
  - Main clues for boards: **cartilage, smooth muscle, and ↑↑goblet cells**

## Thyroglossal duct cyst

- Clinical features
  - Children/young adults; **midline anterior neck**; moves w/ **swallowing**
- Pathogenesis/histopathologic features
  - Columnar, cuboidal or stratified squamous lining with **thyroid follicles** in the wall (low cuboidal epithelium with bright pink contents)
- Comments
  - Main clue for boards: **pink thyroid follicles** (pathognomonic)

## Median raphe cyst

- Clinical features
  - Men; **ventral penis** between urethral meatus and anus
- Pathogenesis/histopathologic features
  - Variable lining of cyst; “**dirty debris**” within cyst; genital skin features (e.g., smooth muscle and small nerves)
- Comments
  - Often presents w/ pain during intercourse

## Branchial cleft cyst

- Clinical features
  - Second or third decades; **lateral neck** (anterior SCM, preauricular, and mandibular)
- Pathogenesis/histopathologic features
  - Pseudostratified columnar or stratified squamous epithelium with surrounding **dense lymphoid tissue** including lymphoid follicles w/ germinal centers
- Comments
  - Main clue for boards: very **prominent lymphoid aggregates/follicles**

## Pseudocyst of the auricle

- Clinical features
  - Middle-aged men; scaphoid fossa
- Pathogenesis/histopathologic features
  - Cystic space in cartilage with fluid, no epithelial lining and no inflammation in cartilage
- Comments
  - a/w chronic **trauma from cell phones** or wrestling

## Omphalomesenteric duct cyst

- Clinical features
  - Umbilical polyp in children
- Pathogenesis/histopathologic features
  - Occurs as a result of a failure to obliterate the connection between midgut and yolk sac during embryogenesis; ectopic columnar gastrointestinal mucosa

## 6.3 MELANOCYTIC NEOPLASMS

### Ephelides (freckles)

- 1- to 3-mm areas of ↑pigmentation; darken w/ sun-exposure; **sun-exposed** areas of body, mainly face, dorsal upper extremities, and upper trunk
- More common in blonde or red haired individuals; absent at birth, but appear in first 3 years of life
- ↑melanogenesis and ↑melanin transfer to keratinocytes
- Histology: ↑basilar keratinocyte pigmentation +/- enlarged melanocytes without increased melanocyte density
- No propensity for malignant transformation, however are a marker of UV damage

### CALM (café-au lait macule)

- Discrete uniform tan to brown macules or patches; may be seen in infants, children, and young adults; isolated finding in 10% to 20% of normal population
- Multiple CALMs may be a/w numerous genodermatoses:
  - **Neurofibromatosis type 1 > type 2**
  - **McCune-Albright syndrome**
  - **Russell-Silver**
  - **Noonan syndrome**
  - **Bloom syndrome**
  - **Tuberous sclerosis**

- MEN-I
- Fanconi syndrome
- Ataxia-telangiectasias
- Histology: ↑melanin deposition in basilar keratinocytes

## Solar lentigo

- Multiple pigmented macules on sun-exposed areas; most common in Caucasians (essentially ubiquitous after 60 years of age) > light-skinned Asians
- Histology: elongated bulbous rete ridges with hyperpigmentation ("dirty socks"); +/- mild increase in melanocyte density; solar elastosis in dermis

## Lentigo simplex

- Well-demarcated, evenly pigmented brown to black macule; any age and any anatomic site
- Histology: basal layer hyperpigmentation; elongated rete ridges with mild ↑melanocyte density
- Conditions a/w multiple lentigines:
  - LEOPARD
  - Carney complex (LAMB/NAME)
  - Peutz-Jeghers (especially oral/perioral)
  - Laugier-Hunziker
  - Cowden syndrome
  - Bannayan-Riley-Ruvalcaba (penile)
  - Xeroderma pigmentosum
  - Cronkhite-Canada

## Mucosal melanotic macule

- Compared with lentigo simplex can be more irregular and mottled
- Oral lesions usually occur in **adults > 40 years old** on **vermillion border** > gingiva, buccal mucosa, or palate; genital lesions most common on labia minora
- Histology: acanthosis; mild basilar hyperpigmentation +/- subtle increase in melanocyte density

## Dermal melanocytosis

- Congenital (Mongolian spot): present at birth in most **Asians and blacks**; **lumbosacral** region; presents with (p/w) gray-blue patch (as a result of the **Tyndall effect** where shorter light wavelengths are reflected by melanocytes); often **resolves** during childhood
  - Histology: sparsely distributed elongated dendritic melanocytes in lower 2/3 dermis, lying parallel to epidermis
- Nevus of Ota: presents in first year of life or around puberty; ↑incidence in pigmented individuals (Asians and blacks); p/w coalescing gray/blue macules in **V1/V2 distribution** and frequent **scleral involvement** (60%); unilateral (90%) > bilateral; persists for life; may **enlarge under hormonal influences**; **10% develop glaucoma**; rare malignant degeneration to **uveal melanoma** (perhaps higher risk in Nevus of Ota lesions with activating mutations in *GNAQ*)
  - Histology: elongated dendritic melanocytes more numerous than in congenital dermal melanocytosis; involves upper dermis

- Other clinical variants:
  - **Nevus of Ito**: located on the shoulder, supraclavicular, and scapular regions; essentially no risk of progression to melanoma
  - **Hori's nevus**: acquired nevus of Ota-like macules **bilateral** zygomatic region; East Asian females
  - **Sun's nevus**: acquired, **unilateral** variant of Hori's nevus
    - Mnemonic: "There is only **1 Sun**, but the (w)Hole face is affected in **HOri's**"
- Histologically, dermal melanocytoses are **distinguished from blue nevi** by their ↓**cellularity**, poor circumscription, and **lack of dermal sclerosis**

## Blue nevus

- Onset in childhood/adolescence, but can also occur in older patients, 25% of cellular blue nevi are congenital
- Most common sites: **scalp, sacral area, and distal extensor extremities**
- Derived from dermal melanocytes (persist during embryogenesis rather than populating epidermis)
- Activating mutations in *GNAQ* and *GNA11* seen in 83%; results in downstream MAPK pathway activation
  - Same mutations are the most common mutations in **uveal melanoma** (46%; concomitant *BAP-1* loss in uveal melanoma leads to increased risk of metastasis and death)
- Multiple blue nevi and epithelioid blue nevi (latter is much more specific) a/w **Carney complex**
- Variants:
  - Common blue nevus:
    - Blue/gray macules or papules usually less than 1 cm
    - Elongated, dendritic melanocytes containing melanin pigment usually in the upper 2/3 dermis with associated **sclerotic collagen**; no junctional component
  - Cellular blue nevus:
    - Blue/gray/black plaques or nodules; often larger (1–3 cm); favor **buttocks or scalp**
    - **Dense proliferation of plump/fusiform pale gray melanocytes** containing little pigment + admixed dendritic melanocytes resembling common blue nevus cells; characteristically bulges into subcutis ("**dumbbell configuration**")
  - Epithelioid blue nevus:
    - Heavily pigmented; usually seen and a/w **Carney complex**; histologically **resembles "animal type melanoma,"** but lacks mitoses and atypia
  - Malignant blue nevus (= melanoma): often arises **within cellular blue nevus; scalp (#1)**; commonly see benign precursor within specimen; frequently have concomitant *GNAQ/GNA11* mutations and *BAP-1* loss (a/w more aggressive behavior, similar to uveal melanoma)

## Recurrent melanocytic nevus

- Repigmentation **confined to the scar** (vs pigment extending beyond biopsy site = melanoma); usually **arises within 6 months** of initial biopsy



- Histology (three key features)
  - Dermal scar
  - Atypical junctional melanocytic proliferation (resembles MIS) confined to area above dermal scar
  - Bland dermal nevus remnants below/adjacent to scar

### Balloon cell nevus

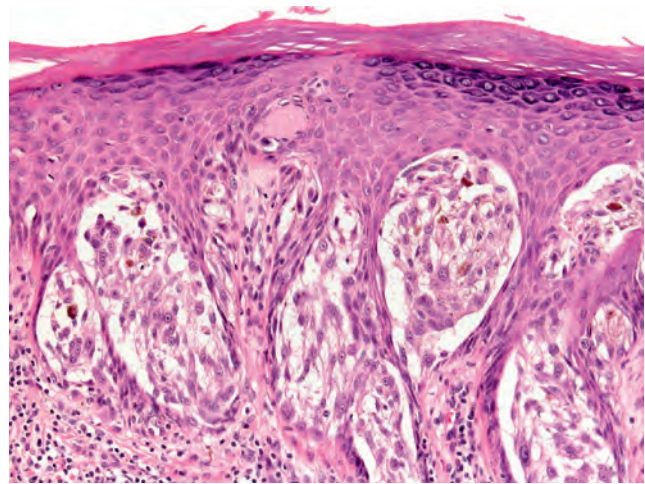
- Clinically indistinguishable from ordinary nevi
- Histology: >50% dermal melanocytes are “balloon cells” (large, pale, and polygonal melanocytes with foamy/vacuolated cytoplasm and variable pigmentation); balloon cell change is as a result of **melanosome degeneration**
  - Boards tip: can always identify conventional nevus somewhere within lesion

### Halo nevus (Sutton nevus)

- Pigmented nevus with surrounding hypopigmented zone; most commonly second decade; most commonly on the **back**; most commonly benign
  - May be a/w vitiligo or melanoma (rarely) at another site
- Multiple lesions can occur idiopathically or w/ infliximab
- Histology: bland nevus w/ **lymphocytes intertwined (“mingling”)** with melanocytes
  - In contrast, lymphocytes form a lichenoid band (“riot police barrier”) under and around melanoma

### Spitz nevus

- Acquired, usually solitary lesions in **first two decades** (use caution in diagnosing a patient in the fourth decade and older); most common on **head/neck** > extremities
- Pathogenesis:
  - **HRAS** mutations/11p gains
  - No **BRAF** mutations
  - Recently described subset of **atypical epithelioid Spitz nevi** with loss of **BAP-1** tumor suppressor gene (“BAPomas”; have unique histology, and unlike most Spitz nevi, have BRAF mutations)
- Rapidly growing pink-red papulonodule; usually <1 cm
- Histology (Fig. 6-5):
  - **Symmetric and circumscribed**; most often compound
  - **Epidermal hyperplasia** (vs consumption of epidermis in melanoma)
  - Large junctional nests with **clefting** around entire nest (vs discohesion of nests in melanoma, where the nest itself becomes fragmented)
  - Parallel “**raining-down**” orientation of nests and cells
  - **Kamino bodies**: pink clumps of BMZ material (collagen IV) within epidermis
  - “**Spitzoid**” cytology: large epithelioid and spindled cells w/ abundant **pink-purple (amphophilic)** cytoplasm and prominent **lilac-colored nucleoli** (vs cherry red nucleoli in melanoma); usually not pigmented



**Figure 6-5.** Histology of Spitz nevus. Nests of cohesive spindled and epithelioid melanocytes with clefts between the nests and the hyperplastic epidermis. (Courtesy, Lorenzo Cerroni, MD) (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

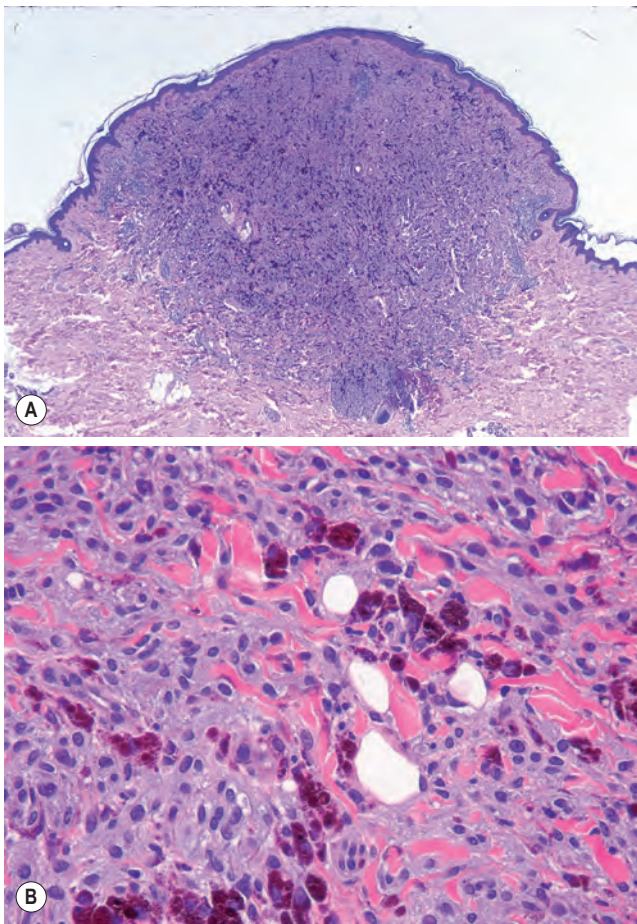
- Dermal component “**matures**” with depth (reduction in density and cell size)
- **Superficial mitoses** allowable, especially in young patients → if numerous (>2–3); deep or atypical mitoses are present, raises concern for melanoma
- Immunostains: **S100A6+**, **S100+**, **Melan-A+**, and **p16+**
  - **p16 is frequently lost/diminished in atypical Spitz tumors and spitzoid melanoma**
- Treatment: controversial, but often complete excision is recommended
- Boards fodder: **FISH analysis very helpful in risk stratification** of atypical Spitzoid lesions
  - **Homozygous loss of 9p21** (most predictive gene locus; corresponds to p16/CDKN2a gene) → ↑risk of metastasis and death

### Pigmented spindle cell nevus of Reed

- Heavily pigmented variant of Spitz nevus comprised **~exclusively of spindled spitzoid melanocytes**
- **Young F > M**; **thigh** most commonly (> other extremities and trunk)
- Darkly pigmented macule/papule, usually <6 mm
- Histology: **junctional or superficial compound**, symmetric, circumscribed proliferation of **spindled melanocytes** arranged in vertically oriented fascicles + **numerous melanophages** (much more than in conventional Spitz nevi) in superficial dermis +/- **pigmented parakeratosis**
  - Architecture: similar to Spitz nevus but almost always **confined to junction** (or very superficial dermis)
  - Cytology: spindled melanocytes are same as in Spitz nevi, but **PSCN lacks the epithelioid cells** seen in conventional Spitz nevi

### Deep penetrating nevus

- Most commonly is a component of combined nevus (overlaps w/ clonal nevus, and inverted type A nevus)



**Figure 6-6.** Deep penetrating nevus. (A) A pigmented melanocytic nevus with a wedge-shaped silhouette is seen. (B) Pigmented spindle and epithelioid melanocytes are present, as well as melanophages. (From Busam KJ. Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology, 2nd edn. Elsevier, 2015.)

- Distinct from blue nevus family based on lack of *GNAQ*/*GNAI1* mutations
- Face, upper trunk and extremities; usually **second and third decades**
- Well-circumscribed blue to black papule; <1 cm in size
- Histology: compound melanocytic proliferation with **minimal junctional component**, superficial **dermal nests resembling ordinary nevus nests** (very helpful clue in distinguishing from cellular blue nevi), and prominent **wedge-shaped dermal component**, which extends deep into the dermis or subcutis, tracks along adnexal structures or neurovascular bundles; **epithelioid pigmented melanocytes** in loose nests with a lot of **melanophages** (Fig. 6-6A and B)
- vs cellular blue nevi: DPN has **junctional component** (always absent in CBN), superficial **dermal nests resembling ordinary nevus nests** (not seen in CBN), **more pigment** within melanocytes (CBN melanocytes are amelanotic → pigment is predominantly in surrounding melanophages), melanocytes are larger and have more cytoplasm

## Congenital melanocytic nevus

- **NRAS mutations** in majority of cases (> *BRAF* mutations)
- Divided into small (<1.5 cm), medium (1.5 cm–19.9 cm), and **large (>20 cm)**
  - Small congenital nevi have same low risk of developing melanoma as conventional nevi
  - Large congenital nevi have **↑melanoma risk** (~2%–3%; majority develop in **first decade**)
- Initially raised tan lesions that may darken over the first year of life; +/- hypertrichosis
- Often develop “**proliferative nodules**” → mimic melanoma clinically and histologically
- **Neurocutaneous melanosis/melanocytosis** = large congenital nevus in association with melanocytic proliferation (benign or malignant) within leptomeninges and brain parenchyma
  - Affects various sites in CNS → variable clinical presentation; **high mortality** in symptomatic patients
- Histology: compound or intradermal melanocytic proliferation; dermal component extends deeper than common acquired nevi; dermal component displays single cell dispersion in deeper dermis, **surrounds/infiltrates vessels, adnexal structures, muscle, and nerve** (not concerning)
- Treatment (large congenital nevi):
  - Surgical resection should be attempted when possible after 6 months of age; if not possible or only partial resection → serial examinations, early biopsies of nodular areas
  - If **large posterior axial congenital nevi** or multiple **satellites** → recommend MRI screening for neurocutaneous melanosis

## Nevus spilus/speckled lentiginous nevus

- Presents within the first year of life
- Homogeneous tan patch within which develops small pigmented macules and papules
- Trunk and extremities most commonly affected sites
- May be associated with **phakomatosis pigmentovascularis** and phakomatosis pigmentokeratotic
- Risk of melanoma is low
- Appears similar to agminated nevus, but the latter occurs in teenage years and with a cluster of nevi over a skin-colored (rather than tan) background

## Common acquired melanocytic nevus

- Most prevalent in Caucasians; may see **eruptive acquired nevi** at affected sites in **epidermolysis bullosa** (“EB nevi”; benign, but often confused for melanoma because of atypical clinical and histologic features) and **LS&A**
- Any site; increase in number over first three decades, then decrease
- “Abtropfung hypothesis”: nevus cells start as junctional proliferation → subsequently migrate into dermis



(compound nevus) → later become entirely intradermal → may involute

- UV exposure; immunosuppression; hormonal influences implicated; **BRAF mutations** in up to 80% (> *NRAS* mutations)
- Clinically well-circumscribed, symmetric, small (<6 mm), and evenly pigmented
- Histology: symmetrically junctional, compound or dermal proliferations w/ small regular nests, and dermal component shows “maturation” with depth (melanocytes become smaller and less nested)

### Atypical (dysplastic) melanocytic nevus

- Occur sporadically or in the setting of familial atypical multiple mole melanoma syndrome (FAMMM)
  - FAMMM: AD inheritance; characterized by multiple melanocytic nevi (50+), family history of melanoma, and mutations in *CDKN2A* gene (encodes p16 and p14<sup>ARF</sup>)
- Any site (**trunk and scalp** most common); wide age range
  - Potential pitfall: new “atypical/dysplastic nevi” on sun-damaged sites of elderly are most likely well-nested LM!
- Solitary or multiple; asymmetric, irregularly bordered, and variably pigmented nevi ranging in size (often >6 mm)
  - When multiple, patients tend to have clinically (and histologically) similar “signature nevi” → melanomas in these patients often appear as “ugly duckling” lesions (different appearance than their signature nevi)
- Histology: classic features of dysplastic (Clark’s) nevus:
  - **Asymmetry**, lack of circumscription
  - Junctional “**shoulder**” (extends ≥3 rete ridges beyond dermal component)
  - Irregular size and placement of junctional nests with **bridging** or **lentiginous pattern** (single-cell junctional growth)
  - Papillary dermal **concentric** and/or **lamellar fibrosis**
  - **Cytologic atypia**: nuclei enlarged (+/- prominent nucleoli), “dirty” gray cytoplasm
  - Significant interobserver variability in grading degree of atypia!
- Treatment: controversial; recent studies support clinical observation of mild and moderately atypical nevi; **severely atypical nevi should be reexcised**
- Prognosis: risk of melanoma directly related to the number of atypical/dysplastic nevi; however, individual dysplastic nevi have **extremely low rate of malignant degeneration**

### Becker’s melanosis (NOT a true melanocytic disorder)

- 0.5% prevalence, more common in adolescent and young adult males
- May be as a result of androgen-mediated hyperplasia
- Onset around **puberty**
- Hyperpigmented plaque with thickening, irregularity, and/or hypertrichosis on **upper torso** most commonly

- **Ipsilateral breast hypoplasia** seen in some patients (Poland syndrome), rarely associated with skeletal defects and/or limb asymmetry
- On histology, **increased basal melanocytes**, epidermal thickening, elongation of the rete ridges, and dermal **smooth muscle hamartoma-like** changes (very difficult to histologically distinguish from smooth muscle hamartoma)

## Melanoma

### Epidemiology

- Most cases in Caucasians; rare cases in dark-skinned individuals (typically acral lentiginous)
- Incidence is increasing; currently the most rapidly rising cancer in Caucasians; trend toward early detection and therefore thinner melanomas
- Wide age range, but mostly fourth decade onward

### Risk factors

- Genetic:
  - **Inherited *CDKN2A* mutations** (FAMMM syndrome; dysplastic nevus syndrome):
    - Protein products **p14<sup>ARF</sup>** and **p16** modulate cell cycle progression via p53 and retinoblastoma (Rb) pathways, respectively
    - Detectable mutations in 25% of familial melanomas
- Other: lightly pigmented skin, UV exposure (cumulative and short intermittent bursts); large number of acquired common and atypical melanocytic nevi, ephelides, and solar lentigines

### Pathogenesis (Boards favorite!)

- **BRAF** (V600E is most common mutation): **non-CSD** (CSD = chronic sun-damaged) sites, **superficial spreading melanomas**
- **NRAS**: chronic sun-damaged (CSD) skin sites, nodular melanomas
- **C-KIT**: **CSD sites**, **acral** and **mucosal** melanomas
- **CCND1/CDK4**: amplifications common on **CSD sites**, **acral** and **mucosal** melanomas
- **GNAQ/GNA11**: **uveal melanoma**, **blue nevi**, and nevus of Ota
- **BAP-1** (BRCA1-Associated Protein 1, a histone deubiquitinase): germline loss-of-function mutations in this tumor suppressor gene lead to increased risk of cutaneous melanoma, **uveal melanoma** and **malignant cellular blue nevi** (both have concomitant *GNAQ/GNA11* mutations; BAP-1 loss is strongly a/w worse prognosis), **epithelioid spitzoid nevi** (“BAPomas;” benign, possess concomitant activating *BRAF* > *NRAS* mutations), and **internal malignancies** (mesothelioma, renal cell carcinoma, and others)

### Subtypes

- **Superficial spreading**: **most common** subtype; may arise de novo or in association with a nevus; peak onset 40 to 60 years old; predilection for **trunk (men)** and **legs (women)**; irregularly shaped/variably pigmented macule during radial growth phase → becomes papulonodular during vertical growth phase

- **Nodular**: onset around sixth decade; most commonly on **head/neck** and back; **M > F**; rapidly growing blue-black nodule; often ulcerated; **lacks horizontal growth phase**; tends to present at a more advanced stage
- **Lentigo maligna**: onset seventh decade and older; **chronically sun-damaged sites** particularly head and neck; presents as an irregularly pigmented brown macule; long horizontal growth phase precedes invasion
- **Acral lentiginous**: less common variant; onset around the seventh decade; **most common type seen in darkly pigmented races**; overall incidence is equal across Caucasians and darkly pigmented races; nail matrix lesions appear as longitudinal melanonychia w/ **Hutchinson sign**; usually presents at an advanced stage because of delayed clinical detection
- **Other less common subtypes**:
  - Desmoplastic melanoma (**Melan-A and HMB-45 negative, S100+, and SOX10+**)
  - Mucosal melanoma
  - Spitzoid melanoma (**homozygous loss of 9p21 detected by FISH → poor outcome**)
  - Uveal melanomas (**GNAQ/GNA11 mutations** = most important driver mutations; very high risk of metastasis if also have concomitant **BAP-1** loss)
  - Malignant blue nevus (**GNAQ/GNA11 mutations** = most important driver mutations; often have concomitant **BAP-1** loss)

### Histologic features

- **General features**: asymmetry, poor circumscription, and irregularly sized and shaped junctional nests with **discohesion** (nest fragments into individual cells); lentiginous/confluent growth along DEJ predominates over nests; pagetoid scatter; **“epidermal consumption”** (melanoma effaces epidermis → epidermal thinning, ulceration); extension down adnexal epithelium; **lack of maturation** of dermal component (sheets of melanocytes and large nests at the base); dermal mitoses; cytologic atypia (irregular, large nuclei w/ **prominent red nucleoli**)
- **Staging parameters**:
  - Most important: Breslow thickness, ulceration, and mitotic rate
  - Others (not always reported): subtype, regression, lymphovascular invasion, host response, microsatellites, and associated nevus (**Tables 6-4 and 6-5**)

### Prognosis

- Variable, depending on stage: >95% 10 year survival for stage IA disease, vs <50% for stage IIIC
- Factors a/w poor prognosis: Breslow >1 mm, ulceration, ↑mitotic rate, ↑age, male gender, palpable lymph node metastases, head/neck/trunk location, and visceral metastases

### Treatment

- WLE or Mohs (mostly LM type), ± sentinel lymph node biopsy (if Breslow depth >1 mm, ulcerated, or ≥1 mitosis)

**Table 6-4.** Melanoma TNM Classification

T Classification	Thickness	Ulceration Status/ Mitoses
Tis	NA	NA
T1	≤1.0 mm	a: without ulceration and mitosis <1/mm <sup>2</sup> b: with ulceration or mitoses ≥1/mm <sup>2</sup>
T2	1.01–2.0 mm	a: without ulceration b: with ulceration
T3	2.01–4.0 mm	a: without ulceration b: with ulceration
T4	>4.0 mm	a: without ulceration b: with ulceration
N Classification	Number of Metastatic Nodes	Nodal Metastatic Mass
N0	0	NA
N1	1 node	a: micrometastasis* b: macrometastasis†
N2	2–3 nodes	a: micrometastasis* b: macrometastasis† c: in-transit met(s)/satellite(s)‡ without metastatic node(s)
N3	Four or more metastatic nodes, matted nodes, or in-transit met(s)/satellite(s)‡ with metastatic node(s)	
M Classification	Site	Serum Lactate Dehydrogenase
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*For defining T1 melanomas, Clark level of invasion is used as default criterion only if mitotic rate cannot be determined. Histologic evaluation of lymph nodes must include at least one immunohistochemical marker (e.g., HMB45, Melan-A/MART-1). NA, not applicable*

*\*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.*

*†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.*

*‡In-transit metastases are >2 cm from the primary tumor, but not beyond the regional lymph nodes; satellite lesions are within 2 cm of the primary. (Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27: 6199–6206. Reprinted with permission from the American Society of Clinical Oncology.)*

- Advanced disease: **anti-PD1/PD-L1 agents** (most promising of the biologic agents for advanced melanoma to date; includes pembrolizumab, nivolumab), BRAF inhibitors, MEK inhibitors, CTLA-4 targeted therapies, and less commonly IFN



**Table 6-5.** Stage Groupings for Cutaneous Melanoma

Survival (%) <sup>*</sup>		Clinical Staging <sup>†</sup>			Pathologic Staging <sup>‡</sup>		
		T	N	M	T	N	M
0		Tis	N0	M0	Tis	N0	M0
IA	97	T1a	N0	M0	T1a	N0	M0
IB	93	T1b T2a	N0	M0	T1b T2a		
IIA	82 79	T2b T3a	N0	M0	T2b T3a	N0	M0
IIB	68 71	T3b T4a	N0	M0	T3b T4a	N0	M0
IIC	53	T4b	N0	M0	T4b	N0	M0
III <sup>§</sup>		Any T	N1 N2 N3	M0			
IIIA	78				T1–4a T1–4a	N1a N2a	M0
IIIB	59				T1–4b T1–4b T1–4a T1–4a T1–4a	N1a N2a N1b N2b N2c	M0
IIIC	40				T1–4b T1–4b T1–4b Any T	N1b N2b N2c N3	M0
IV	9–27	Any T	Any N	Any M1	Any T	Any N	Any M1

<sup>\*</sup>Approximate 5-year survival (%), modified from Balch et al.  
<sup>†</sup>Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.  
<sup>‡</sup>Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception.  
<sup>§</sup>There are no stage III subgroups for clinical staging.  
|| Higher survival rate associated with normal serum LDH levels and lower rate with elevated LDH levels.  
(Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–6206. Reprinted with permission from the American Society of Clinical Oncology.)

## 6.4 ADNEXAL NEOPLASMS AND HAMARTOMAS

- High-yield subject area for dermatology examinations, because of classic histopathologic features

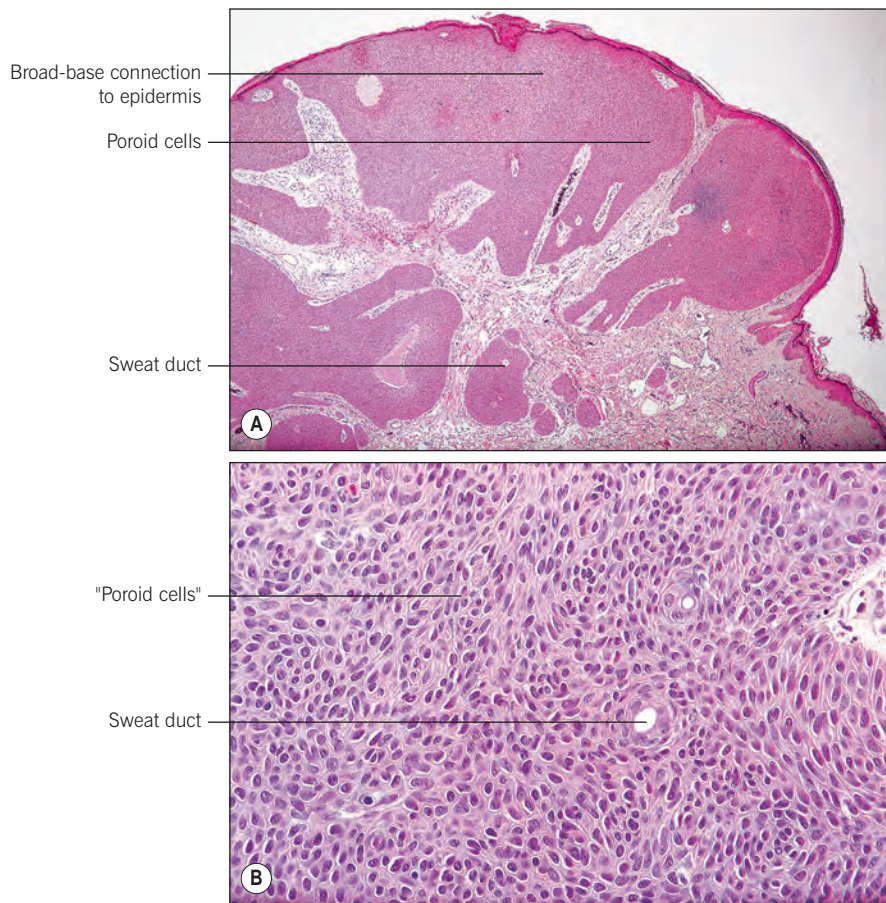
### Eccrine poroma

- Benign sweat gland neoplasm that presents as a **solitary, vascular-appearing** papule/nodule +/- ulceration and **bleeding**; classically surrounded by a **thin moat**; most common sites = **palms/soles** (because of ↑ density of eccrine glands) > head/neck/ scalp; may be a/w nevus sebaceus
  - Poromatosis: widespread or acral eruption of poromas
- Histology: circumscribed **endophytic** proliferation with **broad, multifocal epidermal connections** (Fig. 6-7); comprised of monomorphous “**poroid cells**” (small cuboidal cells with intercellular desmosomal bridges; mnemonic: “poroid cells look like a cute, miniature version of a keratinocyte”); variably sized **sweat ducts** containing a **pink cuticle** encircling luminal aspect of duct; **highly vascularized stroma** resembling granulation tissue
- Immunostains: CEA, EMA, and PAS highlight ducts and intracytoplasmic lumina

- Poroma variants:
  - **Wholly intraepidermal poroma (hidroacanthoma simplex)**: clinically mistaken for SK or SCCIS; most common on **distal extremities**; histology: multiple well-demarcated nests of small poroid cells within the epidermis; ducts may not be easily visualized
  - **Luxtaepidermal poroma (“classic poroma”)**: described previously
  - **Wholly dermal poroma (dermal duct tumor)**: well-circumscribed, “blue balls/nodules within dermis” comprised of poroid cells w/ ducts; lacks epidermal connection
- Malignant counterpart: porocarcinoma
  - **Most common sweat gland malignancy**; elderly (avg 70 years old); most commonly on **lower extremity**; arises within longstanding poroma (11%), de novo, or within nevus sebaceus; **frequent metastasis** (20% to regional LN and up to 10% widespread); **10% mortality**
    - Histology: resembles classic poroma, but has cytologic atypia, ↑ mitoses, atypical mitoses, and **infiltrative growth pattern** at tumor base

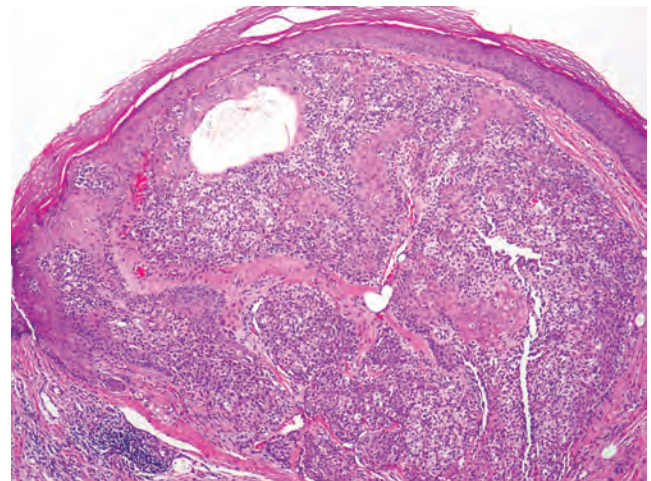
### Hidradenoma

- Benign sweat gland (apocrine > eccrine) neoplasm that presents as a **solitary nodule** (often multilobulated) with a **deep red-purplish hue** and **cystic quality**



**Figure 6-7.** (A) Eccrine poroma (low mag). (B) Eccrine poroma (high mag). (From Rapini R. *Practical Dermatopathology*, 2nd edn. Elsevier, 2012.)

- Histology: circumscribed, **large tumor nodules** +/- **large areas of cystic degeneration**; occupies entire dermis; scattered **sweat ducts** within the tumor nodules; prominent **dermal sclerosis with keloidal collagen (most useful clue!)**; focal epidermal connection (never has broad epidermal connections)
  - Tumor nodules are comprised of **three main cell types** (Fig. 6-8): 1) **squamoid cells**, 2) **poroid cells**, and 3) **clear cells**
    - Any of these three cell types may predominate in a given tumor, but all three are present to some degree
    - **Variants**: clear cell hidradenoma (clear cells predominate), poroid hidradenoma (poroid cells predominate), and solid-cystic hidradenoma (prominent cystic degeneration)
- Malignant counterpart: hidradenocarcinoma
  - Aggressive tumor w/ significant metastatic and death risk; **head/neck (#1 site)**; histology: similar to hidradenoma, but has atypia, numerous mitoses, atypical mitoses, comedo-like necrosis, and lymphovascular invasion; Treatment: Mohs (recent study from Mayo Clinic reported 0% recurrence and 0% metastatic rate), or WLE (up to 75% local recurrence rate and 20%–50% metastatic rate)



**Figure 6-8.** Hidradenoma. Superficial dermal nodulocystic tumor with connections to the epidermis, clear cell features, and squamous metaplasia. (From Busam K.J. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

## Syringoma

- Benign tumor consisting of translucent-skin colored papules; **periorbital region (eyelids #1)**, **cheek** > anterior trunk, genitals; ↑ incidence in **females, Asians**, and in **Down syndrome**
  - Eruptive syringomas (clinical variant): p/w 100s of hyperpigmented small papules on **anterior trunk/**

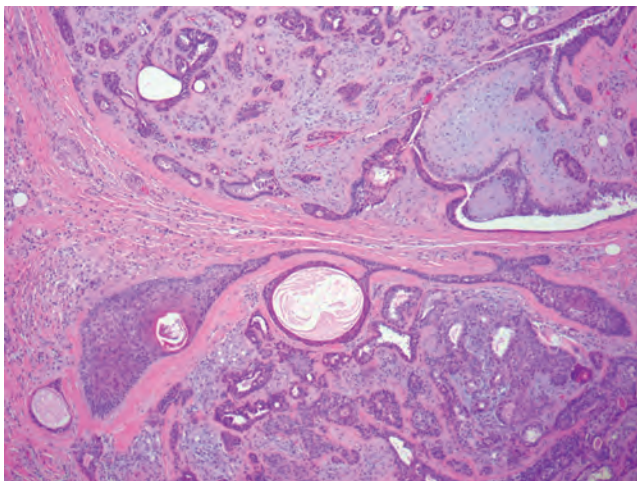


neck; most commonly in Africans/Asians and in Down syndrome

- **Clear cell syringoma** (histologic variant): a/w **diabetes mellitus**
- Histology: circumscribed proliferation of small **tadpole** or **comma-shaped** sweat ducts lined by a thin two cell layer of cuboidal cells; **eosinophilic cuticle** within sweat ducts + **amorphous sweat** within lumen; surrounding **sclerotic stroma**; confined to **upper half of dermis**
- Malignant counterpart = syringomatous carcinoma (eccrine ductal carcinoma and syringoid carcinoma); rare sweat gland malignancy w/ infiltrative growth and minimal cytologic atypia; **always arises de novo**

### Mixed tumor (chondroid syringoma)

- Nonspecific, slow-growing, solitary nodule seen on head/neck (**nose, cheek, and upper lip** > other facial sites); middle-aged adults; M > F; clinically mistaken as cyst
- Comprised of a ~50/50 mixture of **epithelial** (ectodermal) and **stromal** (mesodermal) components → hence, “mixed tumor”
- Appearance of each component is variable:
  - **Epithelial component**: usually **eccrine** or **apocrine** (> follicular, sebaceous, or plasmacytoid)
  - **Stromal component**: **myxoid** or **chondroid** (>collagenous > osteoid or lipid)
- Histology: **circumscribed** dermal/SQ tumor consisting of **glandular structures, ducts, and epithelial strands** with **myxoid/chondroid stroma** (Fig. 6-9)
- Pleomorphic adenoma (oral variant): unlike cutaneous MT, may undergo malignant degeneration with subsequent metastasis
- Treatment: benign; excision is curative
- Malignant counterpart = malignant mixed tumor: extremely rare; very aggressive (50% metastatic rate and 25% mortality); usually arises de novo on distal extremities/foot (uncommon sites for benign MT); Histology: epithelial and/or stromal component appears malignant, w/ infiltrative growth, ↑mitoses, and atypical mitoses



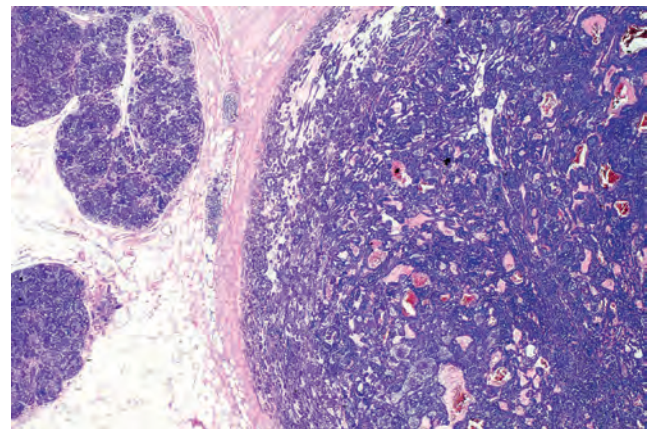
**Figure 6-9.** Benign mixed tumor. A combination of ducts, keratocysts, myo-epithelial cells, and myxoid stroma changes are present. (From Busam KJ. Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology, 2nd edn. Elsevier, 2015.)

### Spiradenoma (“eccrine spiradenoma”)

- Benign **apocrine** neoplasm (despite historical name, “eccrine spiradenoma”)
- Solitary, **painful** dermal or subcutaneous nodule with blue-purple hue; favors **upper half of body**
- Histology: well-circumscribed proliferation of “blue balls in the dermis” w/ **ductal formation** (including **cystically dilated ducts**); tumor nodules are comprised of **biphasic** epithelial cell population: 1) peripheral small blue cells with hyperchromatic nuclei and minimal cytoplasm, and 2) larger, pale-staining inner cells w/ ↑cytoplasm; **intratumoral lymphocytes** (“**lymphocytes peppered in the tumor**” = classic finding!); **PAS+ eosinophilic hyaline droplets** comprised of **BMZ material** (**type IV collagen**) found **within tumor** (same material is found in cylindromas, but typically *encircles* the tumor to form separate jigsaw pieces); very vascular-appearance because of the **widely ectatic vessels** around periphery of tumor and cystically dilated ducts w/ hemorrhage (Fig. 6-10)
- **Brooke-Spiegler syndrome**: AD inherited condition cause by **CYLD mutation**; p/w multiple spiradenomas, cylindromas, trichoblastomas, and trichoepitheliomas
  - **CYLD** (tumor suppressor): normally **binds NEMO** component of I-kappa-B kinase (IKK) complex → inhibits NFκB-mediated resistance to apoptosis
  - In absence of **CYLD**, get ↑NFκB signaling → resistance to apoptosis
- Malignant counterpart = spiradenocarcinoma: very rare, poorly differentiated tumor with aggressive behavior (30% metastatic rate and 20% mortality); **arises within benign spiradenoma**; more common in patients with **Brooke-Spiegler syndrome**; histology: resembles spiradenoma, but **loses its biphasic nature, lacks the characteristic intratumoral lymphocytes**; has ↑mitotic rate; atypical mitoses

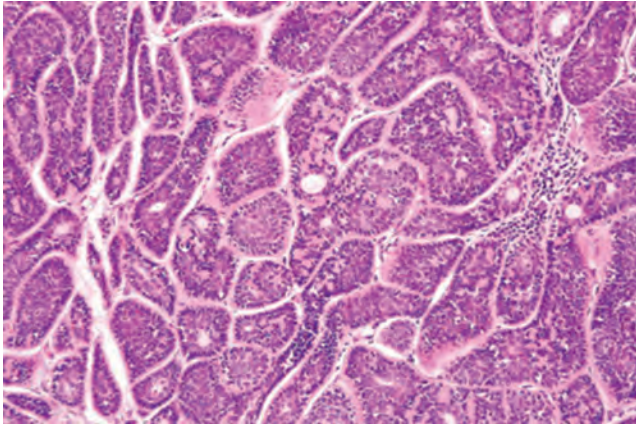
### Cylindroma

- Benign sweat gland neoplasm (**apocrine**) existing on a spectrum w/ spiradenoma; **solitary erythematous-purple**



**Figure 6-10.** Eccrine spiradenoma: in this example, there are three discrete tumor lobules. The largest appears encapsulated. (From Calonje E, et al. McKee’s Pathology of the Skin, 4th edn. Elsevier, 2011)





**Figure 6-11.** Cylindroma. The jigsaw pattern is well developed in this example. Note also the hyaline droplets within the tumor lobules. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)

**nodule** with telangiectasias; 90% occur on head/neck (scalp #1)

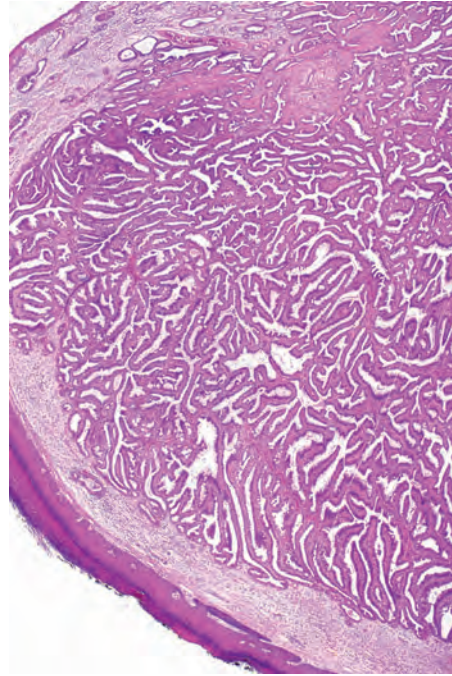
- Multiple cylindromas may coalesce to form multinodular plaques on scalp (“**turban tumor**” in **Brooke-Spiegler syndrome**)
- Histology: well-circumscribed basaloid proliferation comprised of multiple smaller tumor **lobules encircled by thick hyaline BMZ material (type IV collagen)** → multiple small lobules fit together like a “**jigsaw puzzle**”; **biphasic cell population** (same as spiradenoma) with **small ducts** (Fig. 6-11)
- Malignant counterpart = **cylindrocarcinoma**: very rare, poorly differentiated tumor with aggressive behavior (45% metastatic rate); **usually seen in Brooke-Spiegler**; arises within a benign cylindroma; scalp (#1); histology: resembles cylindroma, but **loses biphasic nature**, has ↑mitotic rate, atypical mitoses, infiltrative growth pattern, and neurovascular invasion

### Hidradenoma papilliferum (HPAP)

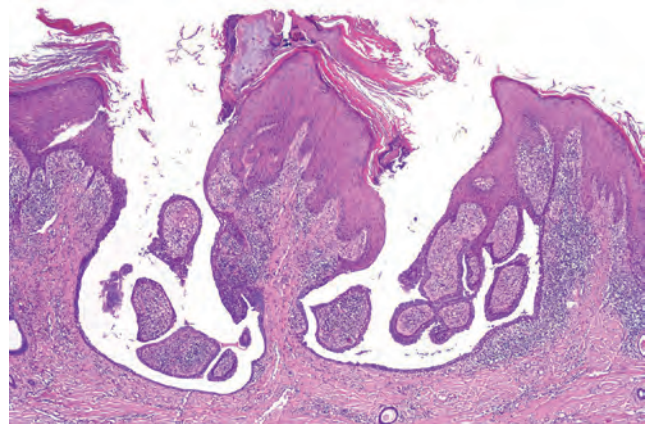
- Benign, painless 1- to 2-cm skin colored nodule; almost exclusively on vulva (**labia majora #1**) of **young adult women**
- Histology: well-circumscribed cystic proliferation in dermis with numerous **papillary projections** with apocrine differentiation invaginating into central cyst-like spaces → “**maze-like**” appearance (Fig. 6-12); **lacks epidermal connection** (major distinguishing feature from SPAP)

### Syringocystadenoma papilliferum (SPAP)

- Benign apocrine neoplasm; presents at **birth or early childhood** with a **solitary, warty papule/plaque** on scalp (> other sites on head/neck > trunk and extremities); usually a/w **nevus sebaceus**
- Histology: **exo-endophytic papillary glandular proliferation** w/ apocrine differentiation; opens onto skin surface; **abundant plasma cells** in peritumoral stroma (Fig. 6-13)
- Malignant transformation is exceptionally rare



**Figure 6-12.** Hidradenoma papilliferum: low-power view of an exophytic ulcerated nodule. The epidermal collarette is seen in the lower left of the field. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)



**Figure 6-13.** Syringocystadenoma papilliferum: this exophytic lesion developed within a nevus sebaceus. Note that the surface is covered with squamous epithelium. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)

### Papillary eccrine adenoma (PEA)

- Benign; **legs (#1)**; favors **black women**
- Histology: well-circumscribed proliferation of **small to medium sized sweat ducts w/ papillary projections** (Fig. 6-14)

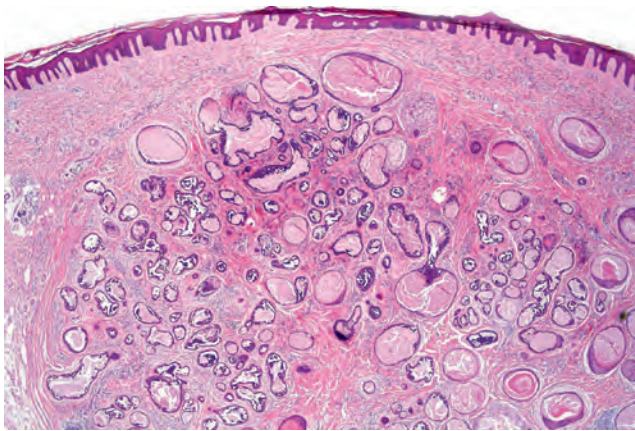
### Tubular apocrine adenoma (TAA)

- Benign; most commonly on **scalp a/w nevus sebaceus**
- Histology: often **indistinguishable from PEA** except for **decapitation secretion**, and ↓papillary projections

### Syringofibroadenoma

- Rare, benign sweat gland proliferation (unclear if true neoplasm or reactive); **legs (#1)**





**Figure 6-14.** Papillary eccrine adenoma: the lesion is composed of dilated ducts and cysts dispersed in a fibrous stroma. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)

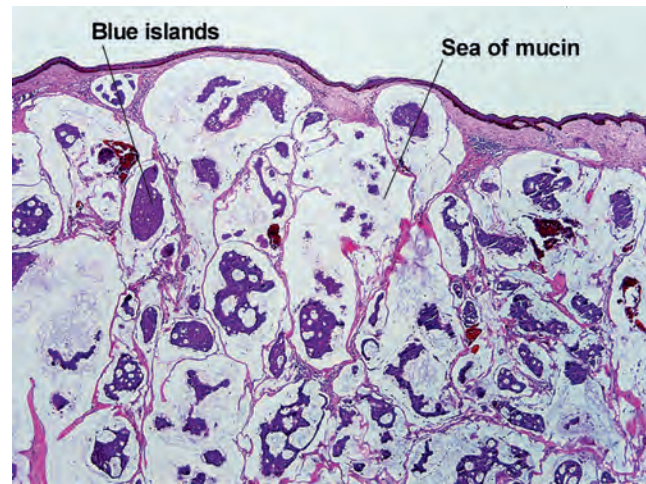


**Figure 6-15.** Middle-aged woman with a typical microcystic adnexal carcinoma. (From Fitzpatrick JE, Morelli JG. *Dermatology Secrets Plus* 4th edn. Elsevier, 2011.)

- May be a/w:
  - Schöpf-Schulz-Passarge
  - Clouston syndrome
  - Chronic stasis dermatitis (reactive process)
- Histology: thin, anastomosing strands of sweat duct-containing epithelium projecting downward from epidermis into mid dermis; rich fibrovascular stroma (similar to poroma)

### Microcystic adnexal carcinoma (MAC, sclerosing sweat duct carcinoma)

- Locally aggressive adnexal carcinoma with divergent/bi-lineage differentiation (follicular + sweat gland)
- Firm, indurated plaque on lip (> chin and cheek) of middle-aged women (Fig. 6-15); Treatment: Mohs (TOC) > WLE (high recurrence rate)
- Histology: poorly circumscribed, deeply infiltrative sclerosing basaloid proliferation with divergent/bi-lineage differentiation (mixture of small sweat ducts + keratinizing "microcysts"); typically has PNI and prominent lymphoid aggregates (most helpful clues on examination); cytologic atypia is minimal



**Figure 6-16.** Mucinous carcinoma. (From Rapini R. *Practical Dermatopathology*, 2nd edn. Elsevier, 2012.)

### Aggressive digital papillary adenocarcinoma

- Rare, highly aggressive malignant sweat gland neoplasm (14% metastatic rate even w/ amputation); affects volar digits of middle-aged adults; M >> F (7:1); Treatment: amputation
- Histology: cystic proliferation with papillary projections, deeply infiltrative growth pattern, cytologic atypia, and ↑mitotic rate; may not always appear overtly malignant, but all cases should be treated aggressively

### Mucinous carcinoma (primary cutaneous)

- Very rare malignant sweat gland neoplasm; presents as a slow-growing, soft nodule; most commonly on eyelid/periorbital region; average age = 60 years old
- Frequent regional recurrences (43% with WLE); rarely metastasizes
- Treatment: emerging data support Mohs (lower reported recurrence rates) over WLE
- Histology: basaloid epithelial tumor nodules "floating in lakes of mucin" (sialomucin); intratumoral ducts give rise to cribriform appearance (Fig. 6-16)
- Clinical pearl: mucinous carcinomas on the face are almost always primary, whereas lesions arising on trunk may represent metastasis of visceral malignancy (GI, breast, lung, or ovarian)

### Adenoid cystic carcinoma

- May arise as a primary adnexal carcinoma or cutaneous metastasis from salivary gland
  - Primary cutaneous ACC: indolent tumor; most commonly on scalp of middle-aged adults; minimal metastatic risk, but up to 70% local recurrence rate (as a result of extensive PNI)
  - Salivary gland ACC: highly aggressive (50% metastatic rate and high mortality)
- Histology: poorly circumscribed proliferation of small to medium sized basaloid tumor nodules w/

cribriform appearance; extends into SQ fat w/ prominent PNI

- May have fibrotic or mucinous stroma (but no large “lakes of mucin”)

## Comparative dermatopathologic features of sweat gland neoplasms for Board Exam purposes

### Poroma (classic juxtaepidermal type)

- Critical histologic features
  - Circumscribed endophytic proliferation with **broad, multifocal epidermal connections**; monomorphic “poroid cells”; “variably sized sweat ducts; highly vascularized stroma
  - Immunostains: CEA, EMA, and PAS highlight ducts and intracytoplasmic lumina
- Most commonly encountered differential diagnosis (DDx)
  - Trichilemmoma: similar endophytic growth pattern, but has **peripheral palisade with thick pink BMZ**, prominent **clear cell change**, and lacks small poroid cells and sweat ducts
  - Hidradenoma: almost entirely confined to dermis, w/ **minimal epidermal connection** (vs broad multifocal connection in poroma); has **three cell types** (poroid + clear cells + squamoid cells); has prominent **stromal sclerosis/hyalinized or keloidal collagen**

### Hidroacanthoma simplex

- Critical histologic features
  - Wholly intraepidermal poroma variant; multiple well-demarcated nests of small poroid cells within the epidermis; sweat ducts may not be easily visualized
- Most commonly encountered DDx
  - Clonal SK, or SK with Borst-Jadassohn effect: cells are at least same size as (often larger than) surrounding k’cytes
  - Bowenoid SCCIS: K’cytes are highly atypical, ↑mitoses, and ↑dyskeratotic k’cytes

### Dermal duct tumor

- Critical histologic features
  - Wholly dermal poroma variant; well-circumscribed “blue balls within dermis”; tumor nodules comprised of poroid cells with same appearance as classic poroma; **lacks epidermal connection**
- Most commonly encountered DDx
  - Hidradenoma: both may look like “big blue balls” in the dermis with sweat ducts; however, hidradenoma is comprised of **three cell types** (poroid + squamoid + clear cells), has prominent **stromal sclerosis/keloidal collagen** around tumor, and has **dilated cystic spaces**
  - Trichoblastoma: both may look like “big blue balls” in the dermis and are comprised of small blue cells, but trichoblastoma has **hair follicle differentiation** with rudimentary hair shafts, papillary mesenchymal bodies, keratin debris, and dystrophic calcification—none of which are seen with dermal duct tumor; TB lacks sweat ducts

- Cylindroma: both appear as blue balls in dermis with sweat ducts, but cylindroma has **thick pink BMZ** material around tumor lobules, **hyaline deposits** within tumor lobules, and **biphasic cell types** (DDT is comprised only of small blue poroid cells)
- Spiradenoma: both appear as blue balls in dermis with sweat ducts, but spiradenoma has **hyaline deposits** within tumor lobules, and **biphasic cell types** (DDT is comprised only of small blue poroid cells), and **large cystic spaces**

### Hidradenoma

- Critical histologic features
  - Circumscribed, large tumor nodules comprised of **three main cell types**: 1) **squamoid cells**, 2) **poroid cells**, 3) **clear cells**; +/- **large cystic spaces** (“solid-cystic hidradenoma”); lesion occupies entire dermis; scattered **sweat ducts**; prominent **dermal sclerosis w/ keloidal collagen** (major clue!); minimal-no epidermal connection
- Most commonly encountered DDx
  - Classic poroma (see above)
  - Dermal duct tumor (see above)
  - Trichoblastoma: both may look like “big blue balls” in the dermis, but trichoblastoma has **hair follicle differentiation** w/ rudimentary hair shafts, papillary mesenchymal bodies, keratin debris, and dystrophic calcification; **lacks sweat ducts**
  - Cylindroma: both appear as blue balls in dermis with sweat ducts, but cylindroma has **thick pink BMZ** material around tumor lobules, **hyaline deposits** within tumor lobules, and **biphasic cell types**; cylindroma **lacks the three cell types** characteristic of hidradenoma; also **lacks stromal sclerosis/hyalinization/keloidal collagen**
  - Spiradenoma: both appear as blue balls in dermis with sweat ducts and dilated cystic spaces; but spiradenoma has **hyaline deposits** within tumor lobules, **biphasic cell types**, “**lymphocytes peppered**” within tumor; spiradenoma **lacks the three cell types** (squamoid, poroid, and clear cells) of hidradenoma and **lacks stromal sclerosis/keloidal collagen**
  - Mixed tumor: both tumors have ducts, a mixture of epithelial cell types, and stromal changes; however, MT has **much more chondroid/myxoid stromal changes** (vs sclerotic collagen/keloidal stroma in hidradenoma)

### Spiradenoma

- Critical histologic features
  - Well-circumscribed nodulo-cystic proliferation of “blue balls in the dermis” with **ductal formation** (often **cystically dilated**); **biphasic** epithelial cell population; intratumoral lymphocytes (“**lymphocytes peppered in the tumor**”); PAS+ eosinophilic **hyaline droplets** comprised of **BMZ material (type IV collagen)** found **within tumor** (same material as in cylindromas, but usually located *within* the tumor, rather than *encircling* the tumor to form separate jigsaw pieces); very **vascular-appearing** because of the **widely ectatic vessels** around periphery of tumor



- Most commonly encountered DDx
  - Cylindroma: thick hyaline BMZ material predominantly **encircles** nodules (vs droplets found *within* nodules, as in spiradenoma) and separates them into small **jigsaw puzzle** pieces; lacks “lymphocyte peppering,” also lacks large cystically dilated ducts and ectatic vascular spaces of spiradenoma
  - Hidradenoma (see above)
  - Dermal duct tumor (see above)

## Cylindroma

- Critical histologic features
  - Well-circumscribed proliferation of multiple small to medium sized **blue tumor lobules** encircled by thick **hyaline BMZ material** (type IV collagen mainly) → leads to “jigsaw puzzle” pattern; scattered **small ducts**; biphasic cell population
- Most commonly encountered DDx
  - Spiradenoma (see above)
  - Dermal duct tumor (see above)
  - Hidradenoma (see above)

## Syringoma

- Critical histologic features
  - Circumscribed proliferation of small **tadpole** or **comma-shaped** sweat ducts w/ **eosinophilic cuticle** and **amorphous** sweat within lumen; sclerotic stroma; confined to **upper half of dermis**
  - Boards fodder: you should **never** see **follicular differentiation** or multiple **horn cysts** in a syringoma → if you see either → more likely DTE or MAC!
- Most commonly encountered DDx
  - DTE: follicular differentiation, horn cysts, and dystrophic calcification; lacks sweat ducts
  - Morpheaform BCC: follicular differentiation, horn cysts, atypical cells w/ ↑mitoses, and apoptotic cells; lacks sweat ducts
  - MAC: like syringoma has sweat ducts, but has concomitant **follicular differentiation** w/ horn cysts (**divergent/bi-lineage differentiation** is a key feature of MAC!), more deeply infiltrative into deep dermis/SQ, PNI w/ lymphoid aggregates (not seen in syringoma)

## Mixed tumor (chondroid syringoma)

- Critical histologic features
  - Tumor/hamartoma of **mixed** epithelial and mesenchymal derivation (hence the name); circumscribed dermal/SQ tumor consisting of **glandular structures, ducts**, and epithelial strands with **myxoid/chondroid stroma**
- Most commonly encountered DDx
  - Hidradenoma (see above)
  - Syringoma: lacks chondroid/myxoid stroma

## Hidradenoma papilliferum (HPAP)

- Critical histologic features
  - Well-circumscribed cystic proliferation in dermis with innumerable **papillary projections** invaginating into

central cyst-like spaces; has “maze-like” appearance; lacks epidermal connection

- Most commonly encountered DDx
  - SPAP: has broad epidermal connection; ↑plasma cells in peritumoral stroma; lacks maze-like quality of HPAP
  - Nipple adenoma/erosive adenomatosis: arises on nipple rather than vulva; typically has connection to overlying epidermis; less maze-like
  - Tubular apocrine adenoma/papillary eccrine adenoma: dermal based proliferation of multiple small ducts w/ papillary projections into lumen; lacks maze-like appearance of HPAP

## Syringocystadenoma papilliferum (SPAP)

- Critical histologic features
  - Verrucous epidermal hyperplasia w/ endophytic growth into dermis; **broadly opens onto epidermis**; papillary projections lined by two cell layers (inner myoepithelial and outer apocrine layer with decapitation secretion); **abundant plasma cells** in peritumoral stroma
- Most commonly encountered DDx
  - HPAP: maze-like quality; lacks epidermal connection

## Papillary eccrine adenoma (PEA)

- Critical histologic features
  - Favors **legs of black women**; well-circumscribed proliferation of **small to medium sized sweat ducts** w/ **papillary projections** extending into the lumen
- Most commonly encountered DDx
  - Tubular apocrine adenoma: nearly identical appearance, but favors scalp; has **decapitation secretion** and ↓papillary projections
  - Aggressive digital papillary adenocarcinoma: more infiltrative growth pattern; ↑mitoses and atypia; occurs on digits

## Tubular apocrine adenoma (TAA)

- Critical histologic features
  - Similar to PEA, but favors scalp; **apocrine differentiation** w/ decapitation secretion and fewer papillary projections
- Most commonly encountered DDx
  - PEA: See above
  - Aggressive digital papillary adenocarcinoma: occurs on fingertips; more infiltrative, ↑atypia and mitoses

## Porokeratotic eccrine ostial and dermal duct nevus

- Critical histologic features
  - Punctate epidermal hyperkeratosis with **cornoid lamellae** arising from **acrosyringium**
- Most commonly encountered DDx
  - Porokeratosis: cornoid lamellae arise from epidermal epithelium, not acrosyringium

## Syringofibroadenoma

- Critical histologic features
  - **Thin, anastomosing strands** of sweat duct-containing epithelium extending down from the epidermis into

the mid dermis; **rich fibrovascular stroma** surrounds tumor

- **Most commonly encountered DDx**
  - Tumor of follicular infundibulum: **follicular** differentiation (lacks sweat ducts); grows laterally in superficial dermis in a “**plate-like**” fashion; multiple connections to overlying epidermis (architecture resembles superficial BCC)
  - Fibroepithelioma of Pinkus: endophytic, bulbous architecture, w/ multiple connections to the overlying epidermis and BCC-like stromal changes; **lacks sweat ducts**

### Microcystic adnexal carcinoma (MAC)

- **Critical histologic features**
  - **Sclerosing basaloid proliferation with divergent/bi-lineage differentiation** (follicular and sweat), giving rise to proliferation of **small sweat ducts** and “**follicular microcysts**”; minimal cytologic atypia; **deeply infiltrative** throughout dermis, SQ and into muscle; typically has **PNI** and **lymphoid aggregates**
  - Boards fodder: mixture of sweat and follicular differentiation (divergent/bi-lineage differentiation) is a very useful clue for MAC; typically do not see this w/ syringoma, DTE, or BCC!
- **Most commonly encountered DDx**
  - Syringoma: both have basaloid tadpole appearance, but syringoma is **circumscribed** (vs infiltrative), **confined to upper half of dermis**, only has **sweat duct differentiation** (lacks follicular elements)
  - Morpheaform BCC: cells more atypical, w/ ↑mitoses, apoptosis, and **myxoid stroma** (vs sclerotic in MAC); only demonstrates follicular differentiation (**lacks sweat ducts**)
  - DTE: follicular differentiation only (**lacks sweat ducts**)

### Aggressive digital papillary adenocarcinoma

- **Critical histologic features**
  - Cystic proliferation w/ papillary projections; deeply infiltrative, cytologic atypia, and ↑mitotic rate
- **Most commonly encountered DDx**
  - PEA, HPAP, and TAA: may have similar low-power appearance, but infiltrative growth pattern and **anatomic site** is critical to diagnosis (Dx) of ADPA!

### Primary cutaneous mucinous carcinoma (PCMC)

- **Critical histologic features**
  - Mnemonic: “**blue tumor islands floating in lakes of mucin**”
  - Immunostaining pattern:
    - Positive: AE1/AE3, CAM5.2, EMA, CEA, CK7, estrogen receptor, progesterone receptor, and +/- neuroendocrine markers (neuron specific enolase, chromogranin, and synaptophysin)
    - Negative: CK20

- Important note: PCMC frequently has an **in situ** component that is identified by finding a **myoepithelial layer** (p63+, SMA+, and calponin+) surrounding the tumor → this **confirms primary cutaneous origin** (rules out metastatic adenocarcinoma from internal organs, since a myoepithelial layer is never present in metastatic tumors)
- **Most commonly encountered DDx**
  - Metastatic mucinous carcinoma from breast: can be ruled out if in situ component of PCMC is found (unfortunately, not always present); otherwise, appears **identical to PCMC** by histologic and immunohistologic studies → need history, examination, and imaging studies; most likely to arise on **trunk** (vs face, which is highly suggestive of PCMC)
  - Metastatic mucinous carcinoma from GI tract: CK7-/CK20+ (vs CK7+/CK20- in PCMC); GI tumors also have a different mucin type than PCMC → can distinguish with mucin histochemistry:
    - **GI tumors = sulfomucin** (Alcian blue positive at pH 1.0 and 0.4)
    - **PCMC = sialomucin** (Alcian blue positive at pH 2.5)
      - ◆ Also may be ruled out if in situ component of PCMC is found

### Adenoid cystic carcinoma

- **Critical histologic features**
  - Poorly circumscribed, infiltrative proliferation of multiple small to medium sized **cribriform** “**blue balls in dermis**” with intratumoral ducts; typically has extension into SQ fat and **PNI**; lacks large “**lakes of mucin**”
- **Most commonly encountered DDx**
  - Mucinous carcinoma: epithelial tumor nodules are **floating in huge lakes of mucin**
  - Trichoblastoma: also appears as “blue balls within dermis” and may also have cribriform appearance, but has **follicular differentiation**; **lacks sweat ducts** and **PNI**
  - Dermal duct tumor: also appears as “blue balls within dermis,” but the proliferation is well-circumscribed; lacks **PNI** and cribriform appearance

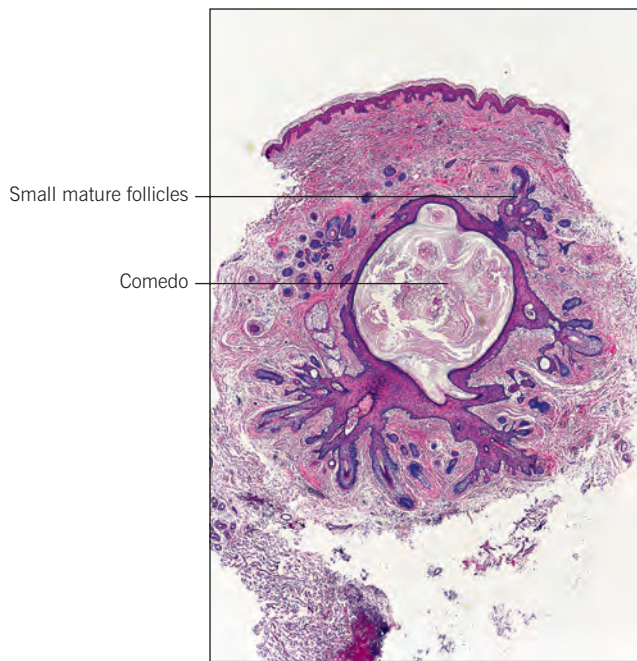
## 6.5 HAIR FOLLICLE NEOPLASMS/HAMARTOMAS

### Folliculo-sebaceous-apocrine hamartomas

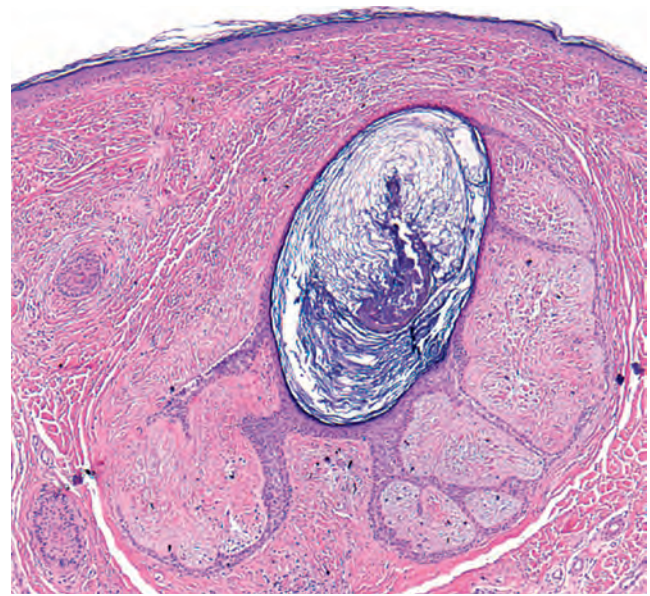
#### Trichofolliculoma

- **Clinical and histopathologic features**
  - Benign follicular hamartoma; skin colored papule w/ **central follicular punctum** from which **numerous tufted vellus hairs** emerge





**Figure 6-17.** Trichofolliculoma (low mag). (From Rapini R. *Practical Dermatopathology*, 2nd edn. Elsevier, 2012.)



**Figure 6-18.** Fibrofolliculomas in association with Birt-Hogg-Dubé syndrome. Histology from a patient with Birt-Hogg-Dubé syndrome showing a mitt-like configuration with a retiform array of isthmic keratinocytes flanked by delicate mucinous stroma. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

- Histology: **dilated central cystic follicle** connected to multiple **fully formed vellus follicles** (Fig. 6-17); background fibrous stroma
- **Sebaceous trichofolliculoma (variant)**: radiating follicles are accompanied by sebaceous glands
- **Folliculosebaceous cystic hamartoma**: likely same entity as sebaceous trichofolliculoma
- **Histologic DDx**
  - **Fibrofolliculoma**: both have a large central follicle with numerous emanating epithelial attachments; however, fibrofolliculoma only has **thin strands** of primitive follicular epithelium (lacks hair shafts)
  - **Pilar sheath acanthoma**: cystically dilated central follicle with radiating **acanthotic epithelium**; no hair shafts in acanthotic buds
- **Other high-yield facts/comments**
  - **Mnemonic**: “multiple baby hairs connected to a large mama hair”

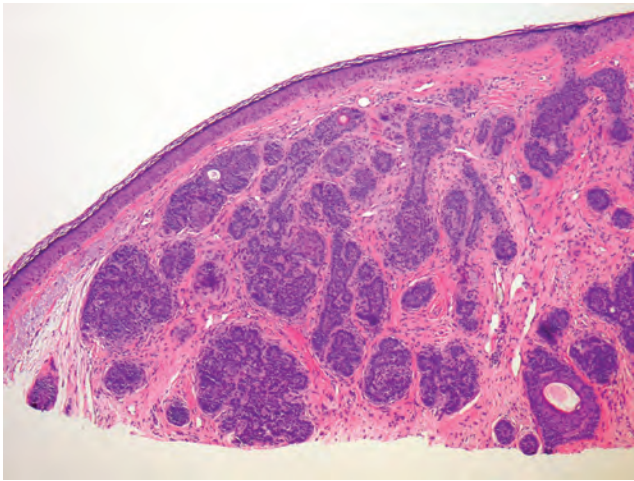
## Fibrofolliculoma

- **Clinical and histopathologic features**
  - Benign hamartoma; nondistinctive, small, skin-colored papules involving **head/neck**; treatment: none required but may try dermabrasion or CO<sub>2</sub> laser ablation
  - Histology: central follicle/cyst with numerous **thin strands of follicular epithelium** radiating from it; lacks hair formation; lesion surrounded by delicate, loose **fibromyxoid stroma** (Fig. 6-18)
  - **Variants (perifollicular fibroma, trichodiscoma, and acrochordons)**: likely same entity, just viewed in different histologic sections; may not visualize the thin strands of follicular epithelium

- **Histologic DDx**
  - **Trichofolliculoma**: has similar central cyst, but attached structures are **fully formed vellus hairs w/ hair shafts**
- **Other high-yield facts/comments**
  - **Birt-Hogg-Dubé syndrome**:
  - Mutation in *FLCN* (encodes folliculin, a tumor suppressor), **AD inheritance**; **triad** of skin lesions (fibrofolliculomas, trichodiscomas, and acrochordons); a/w **RCC**, spontaneous **pneumothorax**, **pulmonary cysts**, and **medullary carcinoma of thyroid**

## Nevus sebaceus

- **Clinical and histopathologic features**
  - Benign hamartoma with follicular, apocrine, and sebaceous components; present **at birth** along **Blaschko's lines**; becomes more yellow and verrucous after puberty; scalp/face most common sites (> trunk and neck); **alopecia** of affected area
  - Histology: verrucous epidermis with malformed, diminutive hairs, **lacks fully formed terminal hairs** within lesion; **sebaceous glands open directly onto skin surface**; **dilated apocrine glands**
- **Histologic DDx**
  - **Epidermal nevus**: appears similar histologically
  - **Sebaceous hyperplasia**: **nodular architecture**; lacks dilated apocrine glands and malformed/diminutive hairs
- **Other high-yield facts/comments**
  - If extensive, may be a/w **Schimmelpenning syndrome** or phakomatosis pigmentokeratotica
  - Secondary adnexal neoplasms arising within nevus sebaceus: **trichoblastoma (#1) > SPAP > trichilemmoma, poroma, TAA, and BCC**

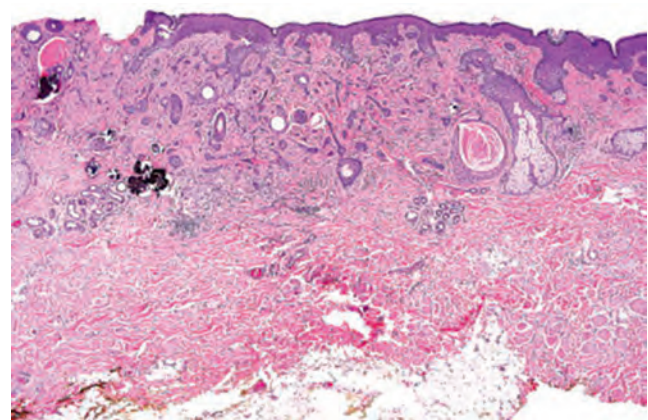


**Figure 6-19.** Trichoepithelioma. Groups of basaloid cells surrounded by fibroblasts forming a fibroepithelial lesion. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

## Neoplasms with follicular germinative differentiation

### Trichoepithelioma

- **Clinical and histopathologic features**
  - Benign; **solitary or multiple** (a/w inherited syndromes) smooth, skin-to-pearly colored, dome shaped papules w/ telangiectasias; **central face** (nose #1, nasolabial folds, upper cutaneous lip, and scalp)
  - **Histology:** well-circumscribed follicular **basaloid proliferation**; well-organized nodules with epithelial fronds, **reticulated strands**, and **cribriform nodules** ("Swiss cheese") (Fig. 6-19); **numerous horn cysts** (much more than BCC); peripheral palisading; **papillary mesenchymal bodies**; **highly cellular fibrotic pink stroma** (fibroblasts account for 50% of tumor's overall cellularity); almost entirely intradermal w/ **minimal to no epidermal connection**; rarely ulcerates; **no clefting** between tumor cells and stroma (stroma is tightly attached to epithelial cells; may have stromal-stromal retraction)
  - **Immunohistochemistry:** scattered **CK20+** Merkel cells within tumor; **PHLDA1+**; **stroma is CD34+** and **CD10+**; **BCL-2** only stains **periphery** of trichoepithelioma (vs diffuse in BCC); androgen receptor negative (vs AR+ in most BCC)
- **Histologic DDx**
  - **BCC:** ↑cytologic atypia, ↑apoptosis, and ↑mitoses; **myxoid stroma** (vs collagenous w/ ↑fibroblasts); lacks cribriform or reticulated architecture; retraction from surrounding stroma; lacks papillary mesenchymal bodies; far fewer horn cysts; has more connection to epidermis; stains: **BCL-2+** (diffuse), **CK20 negative**, **PHLDA1 negative**; stroma is CD10-
  - **Trichoblastoma:** may refer to **large trichoeps** or follicular neoplasms w/ exclusively bulbar differentiation (immature blue cells)



**Figure 6-20.** Desmoplastic trichoepithelioma. Characteristic low-power view showing epithelial strands, cysts, and foci of calcification. There are multiple points of continuity within the epidermis. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 2nd edn. Elsevier, 2011.)

### Other high-yield facts/comments

- Benign follicular tumors are **CK20+** and **PHLDA1+** (new stain) → distinguishes from BCC
- **Syndromes a/w multiple trichoeps:**
  - **Brooke-Spiegler syndrome** (*CYLD* mutation, multiple trichoeps, trichoblastomas, spiradenomas, and cylindromas)
  - **Rombo syndrome** (atrophoderma vermiculatum, hypotrichosis, acro-facial vasodilation and cyanosis, milia, and multiple BCCs)

### Desmoplastic trichoepithelioma

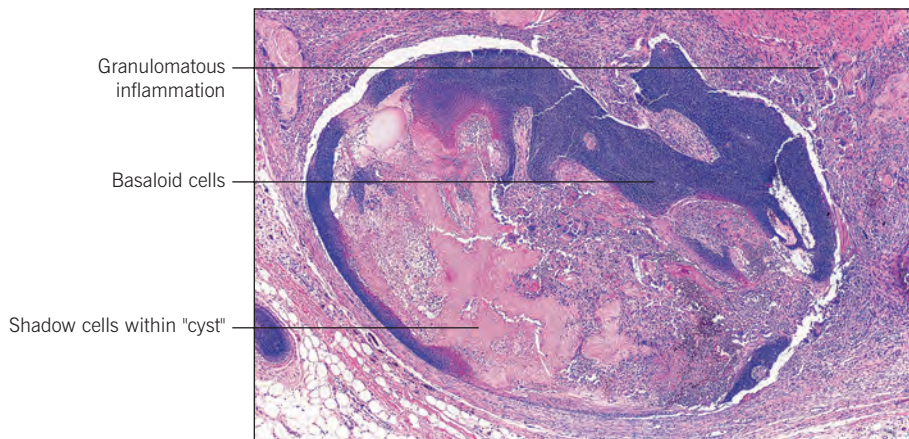
- **Clinical and histopathologic features**
  - **Young adult F > M**; always solitary; almost always on face (cheek #1); **firm annular plaque w/ central dell**
  - **Histology:** well-circumscribed proliferation contained within upper half of dermis; **thin cords** of basaloid cells (2–3 cell layers thick) within **sclerotic/thickened collagenous stroma**; **numerous horn cysts**, **keratin granulomas** (from ruptured microcysts) and **dystrophic calcification** (Fig. 6-20)
- **Histologic DDx**
  - **Morpheaform BCC:** atypical cells w/ ↑mitoses, ↑apoptosis, sharply angled nests, and fewer horn cysts
- **Other high-yield facts/comments**
  - Not a/w inherited syndromes
  - **CK20+** and **PHLDA+** (vs negative in morpheaform BCC)

## Neoplasms with follicular matrix differentiation

### Pilomatricoma (calcifying epithelioma of Malherbe)

- **Clinical and histopathologic features**
  - Solitary, **firm**, flesh colored nodule with **white-chalky hue** from calcification; **cheek (#1)**; **children > adults**; caused by a mutation in the *CTNNB1* gene (encodes β-catenin, involved in WNT pathway)





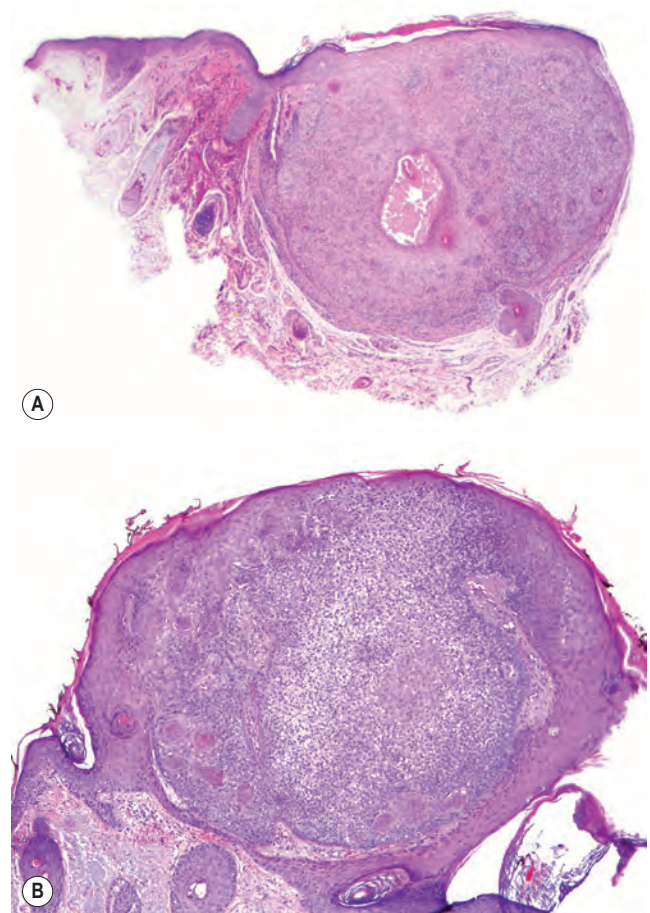
**Figure 6-21.** Pilomatrixoma (low mag). (From Rapini R. *Practical Dermatopathology*, 2nd edn. Elsevier, 2012.)

- **Histology:** well-circumscribed; complex cystic proliferation with internal “rolls and scrolls” appearance (Fig. 6-21); **matrical (basaloid) cells** w/ abrupt transition to fully keratinized, **anucleate “shadow/ghost cells”** (eosinophilic); keratin production leads to intense **granulomatous inflammation**; calcification in 80% (ossification in 20%)
- **Histologic DDx**
  - **Proliferating pilar tumor:** similar convoluted cystic architecture (“rolls and scrolls”), but has **dense eosinophilic trichilemmal keratin** in cyst cavity rather than ghost cells; **lacks basaloid matrical cells**
  - **Pilomatrixal carcinoma:** adults on head/neck; **basaloid cells predominate** over ghost cells; numerous mitoses and infiltrative architecture
- **Other high-yield facts/comments**
  - Old pilomatrixomas may be comprised entirely of ghost cells, with calcification and ossification
  - **Conditions a/w multiple pilomatrixomas:**
    - Myotonic dystrophy
    - Turner syndrome
    - Gardner syndrome (usually multiple hybrid epidermoid cysts with pilomatrical differentiation)
    - Rubinstein-Taybi

## Neoplasms with follicular sheath (trichilemmal) differentiation

### Trichilemmoma

- **Clinical and histopathologic features**
  - Benign; smooth, skin-colored, **verruccous papule** on central face (nose or upper lip most commonly); may arise within nevus sebaceus
  - Histology: circumscribed **lobular proliferation of pale to clear staining cells** containing **abundant glycogen** (resemble outer root sheath cells); **broad epidermal connection, warty surface** w/



**Figure 6-22.** Trichilemmoma. A superficial dermal nodule of small cuboidal keratinocytes with a lobular growth pattern is associated with a follicle. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

hypergranulosis, and **peripheral palisading with eosinophilic/hyalinized BMZ (PAS+)** (Fig. 6-22)

- Immunostains: pan-keratin+ and CD34+ (marker of outer root sheath differentiation)

- **Histologic DDx**
  - Clear cell acanthoma: both are clear cell proliferations arising from epidermis; however, CCA is **not endophytic/lobular** → instead, has regular **psoriasiform hyperplasia** + neutrophils in stratum corneum (mnemonic: “looks like psoriasis with clear cells”)
  - Poroma: similar endophytic/lobular architecture, but is comprised of small blue **poroid cells** + **sweat ducts** + **highly vascular stroma**
  - Verruca vulgaris: lacks clear cells and hyalinized BMZ
- **Other high-yield facts/comments**
  - Multiple trichilemmomas → diagnostic of Cowden syndrome

## Desmoplastic trichilemmoma

- **Clinical and histopathologic features**
  - Always **solitary**; slow-growing flesh-colored papule on **face** (#1 site); often arises within nevus sebaceus
  - **Histology**: mistaken for invasive SCC because has angulated, **pseudoinfiltrative epithelial strands** in **center** of lesion, accompanied by **sclerotic/desmoplastic stroma**; conventional trichilemmoma almost always present at periphery (key to Dx!); tumor is pan-keratin+ and **CD34+** (marker of ORS differentiation)
- **Histologic DDx**
  - Invasive SCC/BCC: lacks conventional TL on periphery, cells appear atypical, w/ ↑mitoses, pleomorphism, and apoptosis
- **Other high-yield facts/comments**
  - **Boards relevance**: they mostly want to see if you can differentiate from SCC
  - Hint: look at periphery to identify conventional trichilemmoma features

## Neoplasms with superficial follicular (isthmus and infundibular) differentiation

### Tumor of the follicular infundibulum

- **Clinical and histopathologic features**
  - Benign; scaly plaque on head/neck
  - **Histology**: **plate-like proliferation** of eosinophilic isthmic keratinocytes arranged in a reticulate fashion in superficial dermis; has broad but intermittent epidermal connections; peripheral palisading
- **Histologic DDx**
  - Superficial BCC: both have broad, intermittent epidermal connections and peripheral palisade, but BCC has clefting; mucinous stroma and cells are more basaloid
  - Eccrine syringofibroadenoma: both have anastomosing or reticulated architecture, but ES has prominent sweat ducts, highly vascular stroma, and deeper extension into dermis
- **Other high-yield facts/comments**
  - Boards: not commonly tested; only the histology could be testable

## Trichoadenoma (of Nikolowski)

- **Clinical and histopathologic features**
  - Benign follicular neoplasm on spectrum with DTE: whereas DTEs have a fairly even mixture of basaloid **follicular epithelial structures** + keratin-filled **microcysts**, trichoadenomas are comprised almost entirely of the **small, keratin-filled microcysts**, with minimal to no basaloid follicular epithelial structures
  - **Histology**: well-circumscribed, superficial dermal proliferation comprised of **small keratinizing milia-like cysts** (“microcysts”) + **sclerotic stroma** (similar to DTE stroma)
- **Histologic DDx**
  - DTE: (see above)
  - Milia: the microcysts of trichoadenoma individually look identical to milia, but simple milia lack the sclerotic stroma of TA
- **Other high-yield facts/comments**
  - Mnemonic: “trichoadenomas look like DTEs that are comprised purely of keratin microcysts”
  - Mnemonic: “trichoadenoma looks like dozens of small milia crammed together in a small biopsy”

## Proliferating pilar (trichilemmal) tumor

- **Clinical and histopathologic features**
  - Discussed in cyst section

## 6.6 SEBACEOUS PROLIFERATIONS

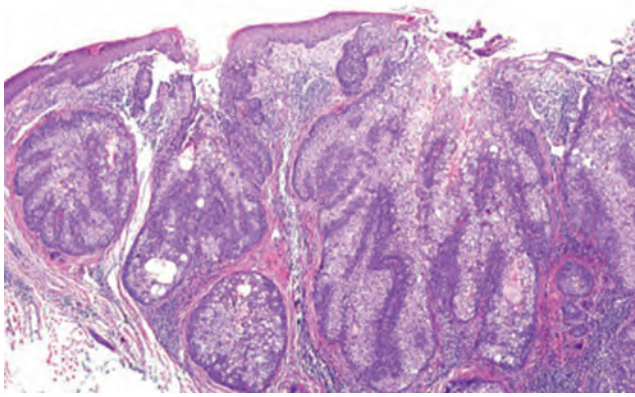
### Sebaceous hyperplasia

- **Clinicopathologic features**
  - Common, benign enlargement of normal sebaceous glands; p/w multiple **yellow papules with central dell** on face and upper trunk
  - **Histopathology**: enlarged sebaceous glands with **normal internal architecture** (peripheral thin layer of immature basaloid **seboblasts** surrounding central, mature, white sebocytes); enlarged sebaceous lobules circumferentially surround a central infundibulum
- **Histologic DDx**
  - Sebaceous adenoma: thicker layer of immature, peripheral, basaloid **seboblasts**; the central sebocytes have cytoplasm that is slightly pinker and more granular than would be expected for a mature sebocyte (should be very white)
- **Other high-yield facts/comments**
  - May assume a linear configuration on clavicle/neck → “juxtaclavicular beaded lines”

### Sebaceous adenoma

- **Clinicopathologic features**
  - Benign, small **yellowish papule** on **head/neck**
  - **Histology**: well-circumscribed, endophytic proliferation with **dilated, direct opening that dumps sebaceous debris onto skin surface** → debris forms impetiginized crust; tumor confined to superficial dermis; tumor is





**Figure 6-23.** Sebaceous adenoma. Part of a well-circumscribed tumor with surface continuity. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)

comprised of sebaceous glands w/ ↑peripheral basaloid seboblasts (30%–50% of tumor) + slightly immature central sebocytes (cytoplasm is pinker and more granular than fully mature, white sebocytes); lacks necrosis, atypical mitoses, and infiltrative growth (Fig. 6-23)

• **Histologic DDx**

- **Sebaceous carcinoma:** ↑seboblasts, ↑mitoses, atypical mitoses, and infiltrative, necrosis
- **Sebaceoma:** Purely intradermal in almost all cases (limited to no connection to skin surface), well-circumscribed nodule comprised of ↑↑ seboblasts (>50%); lacks normal sebaceous gland architecture (vs sebaceous adenoma, which has the same architecture as normal sebaceous glands, but just too many seboblasts)

• **Other high-yield facts/comments**

- Most common sebaceous neoplasm a/w Muir-Torre syndrome
- **Muir-Torre:** AD inheritance; mutation in *MSH2* > *MLH1* > *MSH6*, and *PMS2*; characterized by multiple sebaceous neoplasms; multiple KAs; ↑risk of colon (#1) and GU (#2) cancer

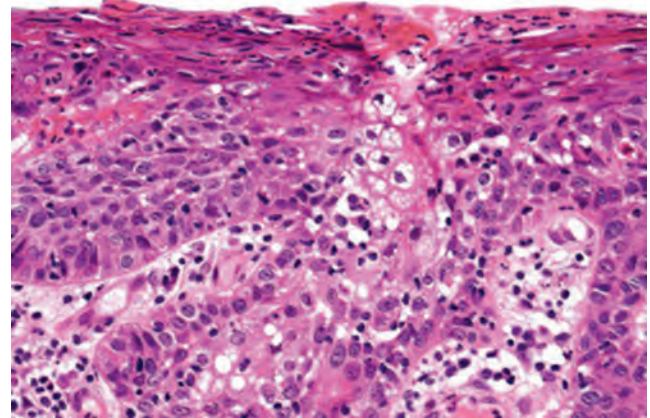
## Sebaceoma (sebaceous epithelioma)

• **Clinicopathologic features**

- Benign; more deeply seated than sebaceous adenoma
- Histology: well-circumscribed, ~entirely intradermal nodule with minimal to no connection to overlying skin surface (vs sebaceous adenoma which dumps open to skin surface); seboblasts are the predominant cell type (>>50%), with a small number of randomly scattered mature sebocytes; lacks the normal sebaceous gland architecture (mature white sebocytes are randomly scattered rather than concentrated centrally); lacks malignant features (cytologic atypia, mitoses, necrosis, and infiltrative growth)

• **Histologic DDx**

- **Sebaceous adenoma:** Opens broadly onto skin surface, dumping its contents/debris onto skin surface; retains normal architecture of a sebaceous gland
- **Sebaceous carcinoma:** has malignant cytologic (nuclear atypia, numerous/atypical mitoses) and



**Figure 6-24.** Sebaceous carcinoma. There is extensive epidermal involvement with conspicuous sebocytes. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011.)

architectural (poorly-circumscribed, infiltrative) features

• **Other high-yield facts/comments**

- Boards tip: if a sebaceous neoplasm has >50% basaloid cells (seboblasts) → must either be sebaceous CA or sebaceoma

## Sebaceous carcinoma

• **Clinicopathologic features**

- Malignant; significant metastatic potential; separated into ocular and extraocular types; most commonly presents as a nonspecific red nodule +/- ulceration; most common sites: periorbital area > other sites on head/neck > trunk
- Histology: asymmetric, infiltrative basaloid proliferation (often >50% seboblasts) w/ ↑mitotic rate, atypical mitoses, and tumor necrosis; arises from epidermis, w/ extension into dermis; ocular sebaceous carcinoma often has prominent pagetoid scatter within epidermis (Fig. 6-24)

• **Histologic DDx**

- Sebaceous adenoma: See above
- Sebaceoma: although it also appears very basaloid with ↑N:C ratio, sebaceoma lacks other malignant features

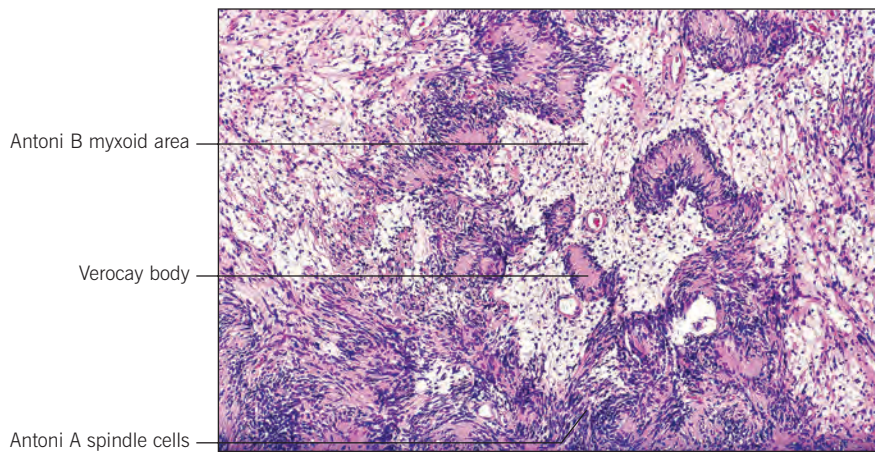
• **Other high-yield facts/comments**

- May be a/w Muir-Torre syndrome or arise de novo
- Ocular form most commonly misdiagnosed as chalazion or blepharitis

## 6.7 NEURAL NEOPLASMS

### Traumatic neuroma

- Reactive proliferation of nerve fibers at sites of trauma → arises from attempted regeneration of nerve
- Flesh-colored firm papule or nodule; painful
- Histology: variably sized/shaped, haphazardly distributed small nerve bundles (resemble normal



**Figure 6-25.** Schwannoma (high mag). (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)

nerves, in that Schwann cells and axonal components are present in a 1 : 1 ratio); background scar

- S100+ and neurofilaments+ (stains axons)

### Palisaded encapsulated neuroma (solitary circumscribed neuroma)

- Adults; most common on face (90%)
- Flesh-colored firm papule
- Histology: **circumscribed dermal nodule w/ clefting at the periphery** (but lacks a true capsule); nodule comprised of tightly packed, fascicular bundles of plump, wavy spindle cells (recapitulates normal nerve; **Schwann cells: axons = 1 : 1**)
  - S100+ and neurofilaments+ (stains axons)
- Histologic DDx:
  - **Schwannoma**: both are fascicular but PEN is way more superficial (Schwannomas arise in deep fat/muscle), has axons (neurofilament stain is negative in Schwannoma), and lacks a true capsule (Schwannoma has EMA+ capsule)
  - **Neurofibroma**: individual cells are similar, but PEN is much more sharply circumscribed and organized as discrete fascicles
- **Multiple mucosal neuromas of MEN 2B (similar histologically)**: multiple pink papules in oral cavity, conjunctiva, and nasal and laryngeal mucosa

### Schwannoma (neurilemmoma)

- Benign proliferation comprised almost entirely of **Schwann cells (S100+)** with **perineurial capsule (EMA+)**
- Solitary pink nodule most commonly on flexural extremities (>head/neck)
- Histology: **deep** (arises in SQ near large nerves), well-circumscribed, **encapsulated** proliferation of plump wavy cells (Schwann cells) with **hypercellular (Antoni A)** areas containing **Verocay bodies** (palisaded nuclei around acellular pink material), and **hypocellular (Antoni B)** myxoid areas; **lacks axons** (vs NF, PEN, traumatic neuromas); may see large nerve from which it arose at periphery (Fig. 6-25)
  - S100+ (stains Schwann cells), EMA+ (stains perineurial capsule); **negative for neurofilaments** (lacks axons)

- Degenerative atypia is present in “ancient schwannomas” (benign)
- **Boards tip**: almost **never** see epidermis in biopsy specimen since so deeply seated (typically appears “shelled-out”)
- 10% of cases are bilateral acoustic neuromas seen in NF-2 patients

### Neurofibroma

- Benign proliferation of Schwann cells + other nerve components (fibroblasts, perineurial cells, intermediate cells, and axons)
- Flesh-colored soft nodule w/ “**buttonhole sign**”
- Histology: dermal location; not as well-circumscribed as PEN; **wavy “buckled” nuclei**; cells haphazardly arranged; **loose, myxoid stroma** with ↑**mast cells** and thin, **wavy collagen fibers**
  - S100+ and neurofilaments+
- 10% have multiple lesions → raises concern for NF1
- **Plexiform neurofibromas (“bag of worms”)**: **pathognomonic of NF-1**; ↑risk of malignant transformation to MPNST

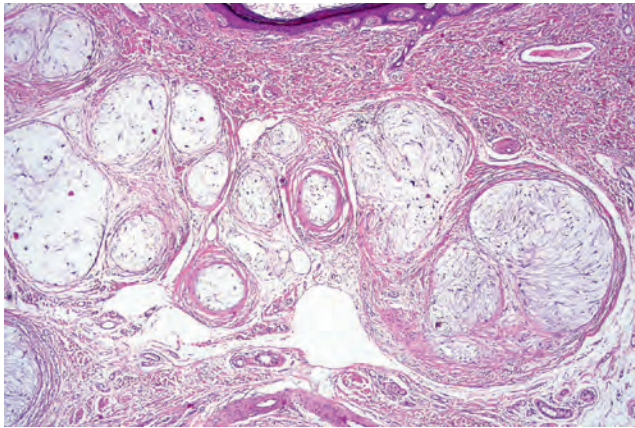
### Nerve sheath myxoma (“neurothekeoma”)

- Formerly called “neurothekeoma” or “myxoid neurothekeoma” → terms have been abandoned and replaced by “nerve sheath myxoma” (preferred current name)
- Soft skin-colored nodule; most commonly **hands/fingers** of 40–50 year old adults
- Histology: **plexiform** proliferation of discrete **myxoid lobules** containing bland spindle cells
  - S-100+ (unlike cellular neurothekeoma) (Fig. 6-26)

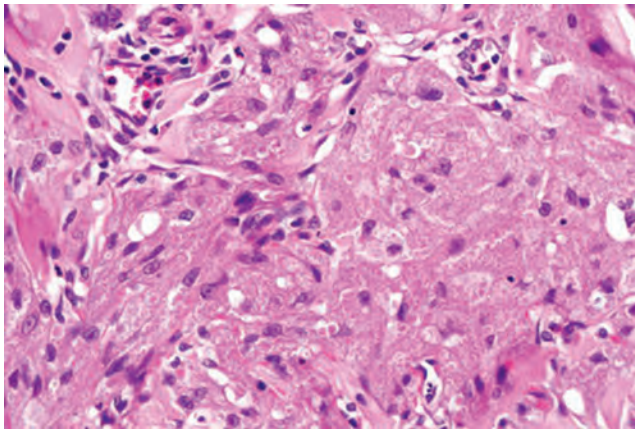
### Cellular neurothekeoma

- Benign neoplasm; uncertain histogenesis
- Firm, pink papules on **face of young adults** (20–30 years old); F > M
- Histology: dermal proliferation; nests and fascicles of **epithelioid cells** (cells resemble Spitz nevus cells or sarcoidal histiocytes)





**Figure 6-26.** Nerve sheath myxoma: the tumor is composed of discrete lobules separated by fibrous septa. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)



**Figure 6-27.** Granular cell tumor. The tumor cells are large with abundant eosinophilic cytoplasm and uniform vesicular nuclei. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)

- Boards favorite: always S-100 negative (vs classic "neurothekeoma"); but S100A6+, NKI/C3+, and PGP 9.5+

## Granular cell tumor

- Benign **neural-crest derived** neoplasm
- Most common in adults (particularly females and African Americans),
- 90% solitary; **tongue (#1)**, but any site affected
- Histology: **pseudoepitheliomatous hyperplasia** overlying an ill-defined dermal proliferation of large polygonal cells with **abundant pink, granular cytoplasm** and a small nucleus, pink cytoplasmic inclusions (**Pustulo-ovoid bodies of Milian** = aggregated lysosomes) (Fig. 6-27)
  - Boards favorite: if see SCC-like epidermal changes → look in dermis for GCT!

## Malignant peripheral nerve sheath tumor

- Presents as a **rapidly growing nodule within a plexiform neurofibroma** (lifetime risk = 2%–13%); may have a large overlying CALM

- Histology: densely cellular proliferation of atypical spindle cells often with large areas of necrosis ("geographic necrosis") and a high mitotic rate

## Merkel cell carcinoma

- Aggressive malignant neoplasm; most common in **elderly on head/neck**; also seen in setting of **immunosuppression**
- Erythematous to **violaceous papulonodule**
- Merkel cell polyomavirus (MCV) implicated
- Histology: infiltrative dermal/subcutaneous mass composed of sheets of uniform basaloid cells with high N:C ratio and finely **speckled "salt and pepper" chromatin** (usually without prominent nucleoli); **numerous mitoses** (often >30/mm<sup>2</sup>) and apoptotic cells
- Positive stains: **CK20 (perinuclear dot pattern)**, **neurofilaments** (perinuclear dot pattern), **chromogranin/synaptophysin**, **neuron-specific enolase**, EMA, and CD56
- Negative stains: **TTF-1**, CK7, S-100, and CEA
- Main DDx is small cell lung carcinoma → immunostains very helpful!
  - **Small cell lung carcinoma**: TTF-1+ and CK7+; negative for CK20, neurofilaments (lacks dot pattern)
- Diameter >2 cm, p63 expression → **worse prognosis**

## Neuroblastoma

- Second most common solid tumor of childhood
- Tumor of primitive neural crest cells of sympathetic nervous system → occurs anywhere neural crest cells migrate (adrenal gland or **retroperitoneum** most common)
- 75% of patients have **metastatic disease at the time of diagnosis**
  - Cutaneous metastases are presenting sign in 30% w/ metastatic disease
  - p/w multiple blue nodules on trunk and extremities
  - Peripheral blanching after stroking lesion, as a result of release of catecholamines
  - **"Raccoon eyes"** (periorbital darkening/purpura) from orbital metastases
- Histology: dermal or subcutaneous nodule comprised of **small, round, blue cells**
  - NSE<sup>+</sup> and neurofilaments<sup>+</sup> → favors neuroblastoma over other small round blue tumors
  - FISH for n-Myc aids in diagnosis; is a/w worse prognosis
- **↑urinary catecholamines (>90%)**
- Infants <1 year old tend to have favorable prognosis, even if metastatic
  - Older children have poorer prognosis

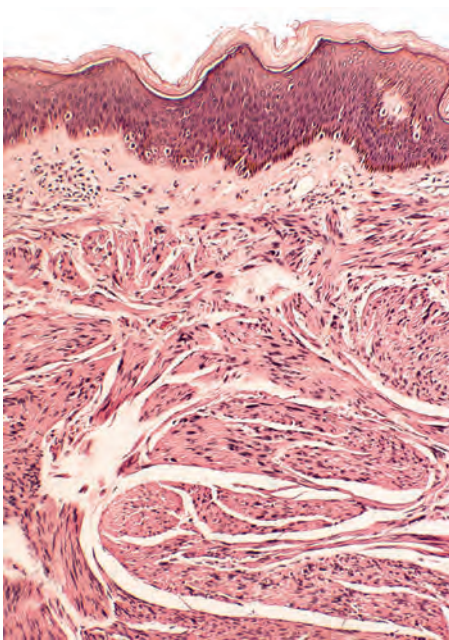
## 6.8 SMOOTH MUSCLE NEOPLASMS

### Pilar leiomyoma

- Benign proliferation of smooth muscle arising from **arrector pili**
- **Red-brown papules on trunk or extremities**
  - **Painful**, especially with cold exposure

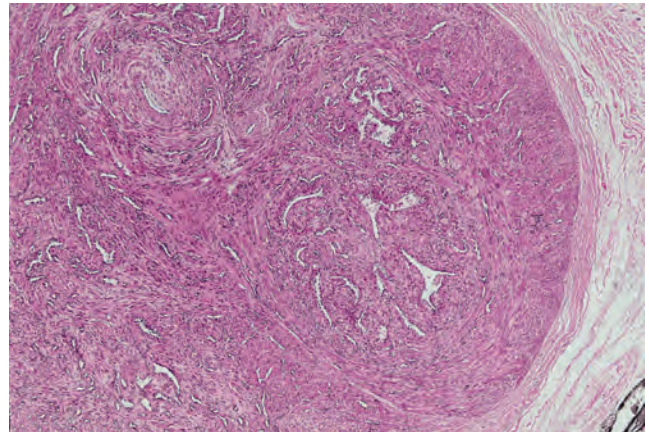


**Figure 6-28.** Leiomyoma. Numerous grouped leiomyomata in a middle-aged woman manifesting as tender erythematous papules on the trunk. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)



**Figure 6-29.** Pilar leiomyoma. The reticular dermis is replaced by interlacing bundles of smooth muscle cells. (H&E) (From Weedon D. *Weedon's Skin Pathology*, 3rd edn. Elsevier, 2009.)

- **Pseudo Darier's sign:** stroking of lesion → becomes red, painful, and elevated (as a result of contraction of smooth muscle)
- Multiple lesions can occur as part of **Reed syndrome** (AD inheritance, **fumarate hydratase mutations**, and multiple cutaneous and uterine leiomyomas and RCC) (Fig. 6-28)
- Histology: ill-defined dermal proliferation of haphazardly arrayed, **intersecting fascicles of smooth muscle cells** (spindle cells with **bright pink cytoplasm** and “cigar-shaped” nuclei), lacks mitotic activity (Fig. 6-29)
  - Stains: **desmin+**, **SMA+**, and **caldesmon+**; smooth muscle fibers are pink-red with Masson trichrome stain



**Figure 6-30.** Angioleiomyoma. (From Weedon D. *Weedon's Skin Pathology*, 3rd edn. Elsevier, 2009.)

#### Box 6-2. Mnemonic

Painful Skin Lesions = “BANGLE(S)”

**B**lue rubber blebs  
**A**ngiolipoma  
**N**euroma  
**G**lomus tumors  
**L**eiomyoma  
**E**ccrine **S**piradenoma

- Histologic DDx:
  - Smooth muscle hamartoma/Becker's nevus: fewer and more discrete smooth muscle bundles interspersed in normal dermal collagen
  - Angioleiomyoma: usually larger and deeper; smooth muscle bundles circumferentially arrayed around collapsed vessels
- Treatment: excision if solitary; if multiple → gabapentin or nifedipine (reduces smooth muscle contraction)

### Genital leiomyoma

- Solitary lesions on the vulva, scrotum, and areola arising from superficial network of smooth muscle found at these sites; asymptomatic
- Histology: similar to pilar leiomyomas, but often **larger**, less sharply circumscribed, and may have mitoses

### Angioleiomyoma

- Benign smooth muscle proliferation derived from smooth muscle in wall of subcutaneous vessels
- Most commonly **middle-aged females** on **lower extremity**; frequently painful (Box 6-2)
- Histology: **Subcutaneous, well-circumscribed nodule** w/ compact fascicles of **smooth muscle cells** **circularly arrayed** around vessels with collapsed (“slit-like”) lumens (Fig. 6-30)
  - Is a proliferation of muscle in vessel wall, not a proliferation of endothelial cells → central **vascular lumens are compressed** by muscular wall →



“slit-like” lumens surrounded by a ton of circularly arrayed smooth muscle

- Stains: **desmin+** (differentiates from myopericytoma), **SMA+**, **calponin+** and **h-caldesmon+**

## Leiomyosarcoma (LMS)

- LMS divided into superficial and deep forms:
  - Deep LMS (subfascial variant): almost never encountered by dermatologists (→ not discussed further); deep soft tissue sarcoma; often arises from smooth muscle walls of large vessels; usually fatal
  - Superficial LMS (suprafascial variant): most relevant variant for dermatologists; arises from arrector pili or genital/areolar smooth muscle; generally **good prognosis**
    - **Dermal LMS**: most behave in indolent fashion, and some experts have argued they are not true malignancies; however, a JAAD 2014 study from Mayo Clinic reported a **10% metastatic rate** with dermal LMS
    - **Subcutaneous LMS**: arises from vascular smooth muscle; **behaves more aggressively** than dermal LMS → ↑risk of metastases (esp. if diameter >5 cm)
- **Red-brown nodules or plaques**; most common on extremities
- Histology: ranges from low-grade (resemble leiomyoma, but have ↑cellularity, ↑mitotic activity, and pleomorphism) to high-grade lesions (AFX-like)
  - Stains: **desmin+** and **SMA+**

## 6.9 HEMATOLYMPHOID NEOPLASMS

### Mycosis fungoides

#### Epidemiology

- Accounts for 50% of all primary cutaneous lymphomas
- Onset typically in sixth or seventh decade, but can occur in younger patients

#### Clinical features

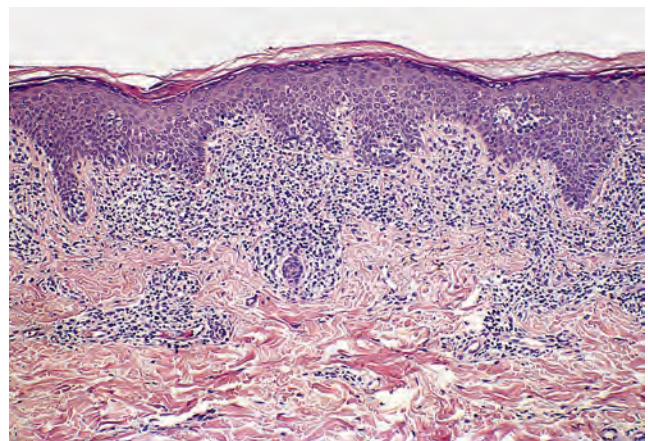
- Progression through patch, plaque, and tumor (in a subset of patients) stages
- Patch stage: irregular erythematous scaly patches occurring in **non sun-exposed/bathing suit distribution**, may be pruritic
- Plaque stage: well-demarcated variably shaped violaceous to red-brown plaques, may be pruritic
- Tumor stage: rapidly enlarging **nodules with frequent ulceration**; arises in a background of patch and plaque lesions (otherwise unlikely to be MF) (Fig. 6-31)
- Rare lymph node and visceral involvement

#### Histology

- Patch stage: **epidermotropic atypical lymphocytes** (enlarged w/ cerebriform, hyperchromatic nuclei) predominantly in the epidermis in clusters (**Pautrier's microabscesses**) and lined up at DEJ with clear halos surrounding the cells; superficial dermal band-like/“lichenoid” lymphocytic infiltrate (predominantly reactive lymphocytes) (Fig. 6-32)



**Figure 6-31.** Mycosis fungoides, tumor stage. Multiple skin tumors in combination with typical patches and plaques. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



**Figure 6-32.** Mycosis fungoides. There is a band-like dermal infiltrate with atypical lymphocytes in the basal epidermis. (H&E) (From Weedon D. *Weedon's Skin Pathology*, 3rd edn. Elsevier, 2009.)

- Clue to epidermotropism (vs exocytosis) = **intraepidermal lymphocytes out of proportion to the degree of spongiosis**
- Plaque stage: **more prominent epidermotropism** w/ more atypical lymphocytes in the dense dermal band-like infiltrate
- Tumor stage: ↑density and depth of dermal infiltrate of atypical lymphocytes with **decreased/absent epidermotropism**
  - Large cell transformation defined by **>25% large cells** (>4 times the size of a mature lymphocyte) +/- **CD30 expression** (often present, but not required for diagnosis) → a/w **poor prognosis**
- Immunophenotype:
  - Typical phenotype: **CD3<sup>+</sup>/CD4<sup>+</sup>/CD8<sup>-</sup>** mature T-lymphocytes
  - **Variable loss of pan T-cell markers**: **CD7 loss most common**, but least specific; **CD5 and CD2 loss less common**, but more specific
- Histologic features are often ambiguous in early patch stage → **molecular testing for T-cell receptor gene rearrangement (TCR-GR)** may be useful
  - However, clonal rearrangements may be detected in some non-neoplastic inflammatory dermatoses (esp.

eczema) → must correlate w/ clinical and histologic findings

- **Hypopigmented MF (variant)**: favors darkly pigmented patients; usually  $CD4^+/CD8^+$  → cytotoxic phenotype → a/w more interface changes (apoptotic k'cytes and pigment incontinence) → explains hypopigmentation seen clinically

### Treatment

- Patch/plaque stage: topical/intralesional steroids, nitrogen mustard, phototherapy, and radiotherapy
- Can add interferon-alpha or retinoids for progressive disease
- Systemic chemotherapy: reserved for advanced/rapidly progressive disease; ↑risk of secondary infections

### Clinical variants

- **Folliculotropic**: 10% of patients; head/neck area a/w alopecia (Fig. 6-33); histology: atypical infiltrates involve follicular epithelium + follicular mucinosis; ↑depth makes it more refractory to treatment → worse prognosis (similar to tumor stage MF)
- **Pagetoid reticulosis (Woringer-Kolopp disease)**: rare, progressive solitary psoriasiform plaque on distal extremities; histology: very prominent epidermotropism in a pagetoid pattern; good prognosis
- **Granulomatous slack skin**: extremely rare; sagging skin folds in the axilla/groin; granulomatous inflammation w/ multinucleated giant cells, atypical lymphocytes, and prominent elastophagocytosis (→ loss of elastic recoil); indolent course; usually evolves to classic MF; up to 30% develop Hodgkin's lymphoma

### Sézary syndrome

- Erythroderma (intensely pruritic); lymphadenopathy and neoplastic Sézary cells in the skin, blood, and lymph nodes; considered distinct from mycosis fungoides
- Must demonstrate a circulating population of  $CD4^+$  neoplastic T-cells with an absolute count  $>1000$  cells/ $\mu$ L
- Histologic features may be nonspecific or resemble MF
- Poor prognosis



**Figure 6-33.** Alopecia mucinosa. (From Andrews et al. *Andrews' Diseases of the Skin*, 12th edn. Elsevier, 2016.)

### Adult T-cell leukemia/lymphoma (ATLL)

- a/w HTLV-1 virus → endemic in areas with high virus prevalence (Japan, Caribbean, central Africa)
- p/w leukemia, lymphadenopathy, organomegaly, hypercalcemia, and skin lesions; poor prognosis
- Histopathology resembles MF, but has characteristic "floret" or "clover-leaf" malignant T-cells
  - Immunophenotype:  $CD4^+/CD8^-/CD25^+$

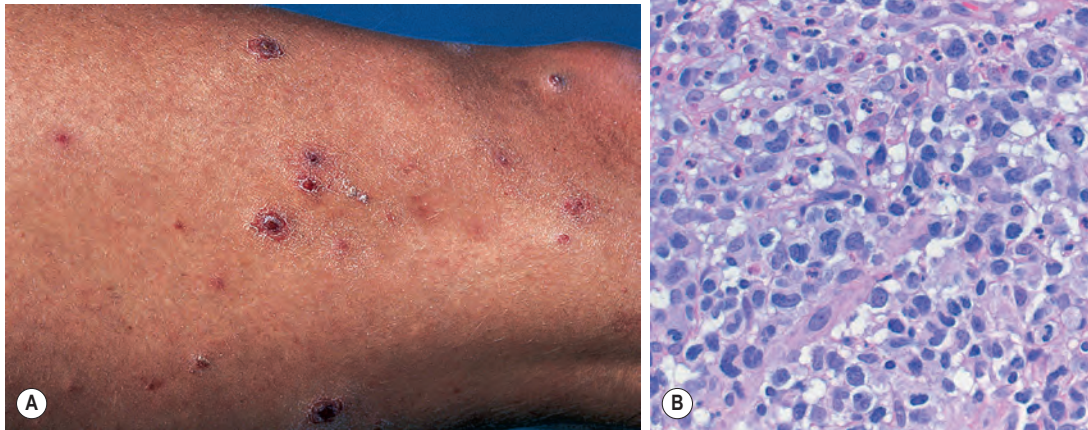
### Lymphomatoid papulosis (LyP)

- **CD30+ lymphoproliferative disorder**; classified as an indolent lymphoma by WHO
- Any age, but favors adults in 40s (vs PLEVA, which favors children); multiple (10–20 lesions usually), recurrent, ulcerative, and red-brown papulonodules on trunk and extremities → individual lesions self-resolve in 1 to 2 months → heals w/ atrophic varioliform scars (Fig. 6-34A)
- Histology
  - **Type A (75%)**: wedge-shaped infiltrate with clusters of large, atypical, Reed-Sternberg-like  $CD30^+$  (Ki-1) lymphocytes, ↑mitotic activity and atypical mitoses, mixed inflammation (lymphocytes, eosinophils, and neutrophils); overlying ulceration and parakeratotic scale (Fig. 6-34B)
  - **Type B (10%–15%)**: resembles patch/plaque MF
  - **Type C (10%)**: dense pan-dermal infiltrate with sheets of  $CD30^+$  large lymphocytes; histologically indistinguishable from ALCL and large cell transformation of tumor-stage MF → need clinical correlation
  - **Type D ( $<5\%$ )**: epidermotropic  $CD8^+/CD30^+$  cells; histologically resembles aggressive epidermotropic T-cell lymphoma, but has much better prognosis → need clinical correlation to ensure correct diagnosis
- TCRG clonal rearrangement in 50% (not correlated w/ biologic behavior)
- Excellent prognosis ( $>98\%$  survival)
- Treatment: only treat if symptomatic, because treatment does not prevent secondary lymphomas; MTX → dramatic improvement in 90%
- **Boards pearls**
  - Type A LyP is distinguished from PLEVA by presence of large  $CD30^+$  cells, and "dirty infiltrate" containing numerous eosinophils (never seen in PLEVA) and neutrophils
  - 20% have antecedent, concurrent, or subsequent lymphomas (MF  $>$  ALCL  $>$  Hodgkin's lymphoma)
  - Dermal hypersensitivity reactions (scabies, bug bites, and drug reactions) often have scattered  $CD30^+$  cells → may histologically mimic LyP

### Primary cutaneous ALCL (anaplastic large cell lymphoma)

- Solitary ( $>$  multiple) ulcerated tumors up to 10 cm (larger than LyP); usually adults; unlike LyP, lesions do not rapidly "come and go"
- Frequently persists/relapses in skin; rare nodal involvement





**Figure 6-34.** Lymphomatoid papulosis (LyP). **(A)** Clinical presentation with papulonecrotic skin lesions at different stages of evolution. **(B)** Diffuse infiltrate with many large atypical lymphocytes. Scattered neutrophils are seen both in the epidermis and dermis. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

- Histology: **sheets** of large, atypical CD30<sup>+</sup> lymphocytes comprising >75% of infiltrate; majority are CD4<sup>+</sup>
- **Lack ALK translocations** (vs systemic ALCL); EMA negative as well
- Excellent prognosis (90% 5 year survival)

### Subcutaneous panniculitis-like T-cell lymphoma

- Lymphoma composed of CD4<sup>−</sup>/ CD8<sup>+</sup>/ CD56<sup>−</sup>/ TIA1<sup>+</sup>/ Granzyme B<sup>+</sup> (cytotoxic) T-lymphocytes with  $\alpha/\beta$  phenotype
  - Category previously included aggressive forms now re-classified as  $\gamma/\delta$ -delta T-cell lymphoma (universally fatal)
- Any age affected; generalized **subcutaneous nodules** on **legs and trunk**
- Histology: subcutaneous lobular infiltrate of **neoplastic T-cells that “rim” adipocytes**; prominent necrotic debris and **cytophagocytosis (“beanbag cells”)**; lacks interface changes at DEJ (vs  $\gamma/\delta$ -delta T-cell lymphoma) and lacks nodular lymphoid aggregates and germinal center formation (vs lupus profundus)
- **Good prognosis** (80%–90% 5 year survival)

### Primary cutaneous $\gamma/\delta$ T-cell lymphoma

- Aggressive CD4<sup>−</sup>/CD8<sup>−</sup> (“double negative”) T-cell lymphoma w/ expression of  $\gamma/\delta$  T-cell receptor and cytotoxic markers (CD56<sup>+</sup>, TIA-1<sup>+</sup>, granzyme B<sup>+</sup>, and perforin<sup>+</sup>)
  - **$\beta$ -F1 negative** (vs SPTCL, which is  $\beta$ -F1<sup>+</sup>)
- Multiple eroded nodules and plaques + visceral involvement

- Histology: dense dermal and subcutaneous lymphoid infiltrate w/ **epidermotropism**, **lichenoid interface changes (major clue)**, vascular destruction, +/- **fat rimming** (mimicking SPTCL)
  - Lichenoid interface changes distinguish from SPTCL (never has epidermal involvement)
  - Lupus profundus is extremely hard to distinguish →  $\gamma/\delta$  stain is helpful; also lupus tends to have reactive lymphoid follicles (uncommon in  $\gamma/\delta$  TCL)
- Rapidly fatal

### Extranodal NK/T-cell lymphoma, nasal type

- EBV<sup>+</sup> lymphoma with **NK phenotype**
- Abrupt onset of **ulcerated tumors**, most commonly on **nasal region**
- Histology: variably sized neoplastic cells with prominent **vascular destruction**
- CD2<sup>+</sup>/CD56<sup>+</sup> and CD3<sup>+</sup> (cytoplasmic, not surface)
- Usually fatal

### Aggressive epidermotropic cytotoxic (CD8<sup>+</sup>) T-cell lymphoma

- Old name = Ketron-Goodman type of pagetoid reticulosis
- Eruptive ulcerated tumors with visceral involvement
- Histology: malignant, cytotoxic, CD8<sup>+</sup> infiltrate with prominent epidermotropism and angiodestruction
  - Histologically indistinguishable from other epidermotropic CD8<sup>+</sup> lymphomas (MF, pagetoid reticulosis, and type D LyP) → distinction best made clinically
- Usually fatal

**Table 6-6.** Cutaneous B-cell Lymphomas

	Clinical Features	Histopathologic Features
Primary cutaneous follicle center cell lymphoma	Violaceous, usually solitary papule or nodule on the <b>scalp/forehead or back</b> (" <b>Crosti's lymphoma</b> "); <b>excellent prognosis</b>	Irregularly shaped neoplastic follicles; lacks a well-defined mantle zone and <b>tingible body macrophages</b> - Usually <b>lacks t(14;18)</b> IgH-Bcl-2 translocation characteristic of systemic follicular lymphoma - <b>BCL-6(+)</b> and <b>BCL-2(-)</b>
Primary cutaneous marginal zone lymphoma	Purple to brown nodule on the upper extremities or trunk; <b>excellent prognosis</b>	Nodular dermal infiltrate with prominent <b>monocytoid B-cells</b> (small lymphocytes with clear halo) and often <b>numerous plasma cells (major clue)</b> , some with <b>Dutcher bodies</b> - <b>BCL-6(-)</b> and <b>BCL-2(+)</b>
Primary cutaneous diffuse large B-cell lymphoma, leg type	<b>Elderly</b> , F > M; red to brown nodule on <b>distal extremity (leg #1)</b> , but can occur at other sites; must exclude systemic disease; <b>less favorable prognosis</b> (5 year survival = 50%)	<b>Dense sheets</b> of large round, <b>markedly atypical lymphocytes</b> w/ mitoses and apoptotic debris in dermis and possibly subcutis; Grenz zone - <b>Bcl-2+</b> , <b>BCL-6+</b> (most cases), and <b>MUM-1+</b>
Intravascular B-cell lymphoma	Purple patches and plaques; trunk/thighs; usually <b>systemic involvement including CNS</b> (→ <b>neuro deficits</b> ), but can be limited to the skin	Large atypical <b>CD20+ B-lymphocytes within vessels</b>

### Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma

- Presents as a **solitary** plaque or nodule on the **head/neck** (> upper trunk) with an **excellent prognosis**
- Histology: dense dermal/subcutaneous infiltrate of small to medium lymphocytes; minimal to no epidermotropism; MF-like immunophenotype (CD4<sup>+</sup>/CD8<sup>-</sup>/CD30<sup>-</sup>)
- **Histologically indistinguishable from tumor stage MF** → need clinical correlation (lacks preceding MF patches/plaques)

### Primary cutaneous B-cell neoplasms

- B-cell neoplasms limited to the skin after systemic workup (except intravascular B-cell lymphoma); relatively less common than T-cell neoplasms
- IgH clonality studies are useful in differentiating low-grade B-cell lymphomas from cutaneous lymphoid hyperplasia
- Typically **CD20+** and **CD79a+** (Table 6-6)

### Leukemia cutis

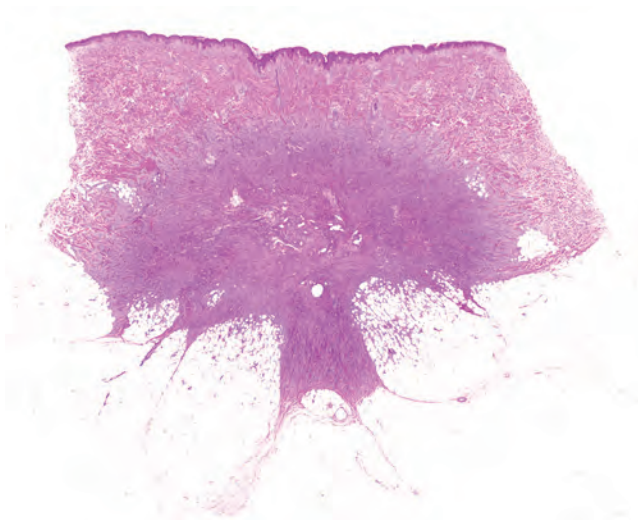
- Most commonly acute myeloid leukemia
  - Generally there is preceding marrow and peripheral blood involvement, but aleukemic forms can occur
- Violaceous papules and nodules at any location
- Skin involvement is **most common with myelomonocytic and monocytic types**
- Histology: Grenz zone, diffuse dermal infiltrate of **myeloid blasts** (monotonous cells with high N:C ratio and fine chromatin); may be seen in sheets, nodules, perivascularly, or as infiltrative cords ("**Indian-filing**")
- **MPO+**, **CD117 (c-KIT)+**, **CD13+**, **CD33+**, and **CD34+**
- Boards fodder: chloromas appear as green nodules in the setting of AML, because of myeloperoxidase activity

## 6.10 FIBROHISTIOCYTIC NEOPLASMS

### Dermatofibroma

- Common benign fibrohistiocytic lesion; favors adults (F > M); most commonly on **lower extremities**
- Firm dermal papules w/ **overlying pigmentation** and "**dimple**" sign (moves downward when pinched)
- Unclear pathogenesis, may be related to prior trauma/bug bite
- Histology: **dermal spindle cell proliferation** with whorled/curly Q pattern, peripheral collagen trapping, admixed inflammatory cells, **Touton-type giant cells** that may contain **hemosiderin**, **overlying epidermal hyperplasia** ("tabled rete"), **basal hyperpigmentation** and **folliculosebaceous induction**; frequently abuts but **never deeply infiltrates fat**
  - Immunophenotype:
    - Positive: **factor 13a**, CD10 (strong, diffuse), **stromelysin-3** (distinguishes from DFSP) and D2-40 (recent study showed positivity in 100% of DF and cellular DF vs. 0% in DFSP)
    - Negative: **CD34**, S100, and pan-keratin
- Key distinguishing features of DF (vs DFSP):
  - Collagen trapping (**best appreciated at periphery**)
  - Touton-type giant cells and foamy histiocytes (never seen in DFSP)
  - Hemosiderin-laden histiocytes/Touton giant cells (never seen in DFSP)
  - **DF only "flirts" with upper part of fat, but never penetrates it deeply (Fig. 6-35)**
  - Epidermal and folliculosebaceous induction (rarely seen in DFSP)
  - Factor 13a+, Stromelysin-3+, and CD34 negative
- DF variants:
  - Cellular DF: ↑cellularity, cells arranged in longer fascicles; most common type to be confused w/ DFSP (see above clues)





**Figure 6-35.** Cellular dermatofibroma (cellular benign fibrous histiocytoma). Stellate-shaped lesion that extends into the superficial subcutis along fibrous septa. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

- Hemosiderotic: prominent hemosiderin and small blood vessels
- Lipidized/xanthomatous: prominent foam cells
- Aneurysmal: large cavernous vascular spaces; clinically worrisome for melanoma or malignant vascular lesion
- DF with “monster” cells: contains large, bizarre, and highly pleomorphic cells; mitoses are rare, never see atypical mitoses
- ↑risk of local recurrence w/ aneurysmal, atypical, and cellular DFs → reexcision recommended

### Dermatofibrosarcoma protuberans

- Tumor of intermediate malignant potential characterized by **t(17;22) COL1A1-PDGFB fusion**
  - Most common abnormality: **supernumerary ring chromosomes** (chr22 most commonly)
- Young to middle aged adults; M ≈ F; favors **trunk** (shoulder #1), **proximal extremities**, and **groin** >> head/neck
- **Mnemonic:** “DFSP affects people 17 to 22 years old Called Pat” → helps remember young age (17–22) and the order of the fused genes (17 = COL1A1; 22 = PDGFB)
- Firm plaque that expands and develops multinodular appearance (Fig. 6-36)
- Histology: **monotonous** spindle cells (cells are more bland and uniform than DF!) with a **storiform** architecture in dermis and throughout SQ fat; characteristic “**honeycomb**” infiltration of fat
  - **CD34 strongly positive**
  - Negative for factor 13a, stromelysin-3, and D2-40 (positive in 100% of DF)
- **Fibrosarcomatous degeneration:**
  - Occurs in 9% to 20%



**Figure 6-36.** Congenital dermatofibrosarcoma protuberans of the back at presentation in a 16-year-old boy, featuring various morphologic clinical features, including plaques, nodules, atrophy, telangiectasia, and scar-like changes. (From Johnson-Jahangir H, Ratner D. *Advances in Management of Dermatofibrosarcoma Protuberans*. *Dermatol Clin*. 2011 April 1;29:2:191–2001)

- Histology: ↑cellularity, ↑mitoses, ↑atypia, “**herringbone pattern**,” and ↓**CD34 staining** (weak or lost)
- Recent study (Hoesly et al., JAAD 2015) showed ↑**recurrence rate** and ↑**metastasis** (18% vs 0% for conventional DFSP) for lesions with fibrosarcomatous change
- Treatment: **Mohs (TOC)** > WLE w/ 2 cm margins
  - **Imatinib** is approved for unresectable or metastatic disease (46% partial response rate) → blocks activity of COL1A1-PDGFB fusion protein
- Prognosis: propensity for **local recurrence** (1% with Mohs; average of 15% w/ WLE; up to 50% recurrence with WLE for head/neck lesions); very low risk of metastatic disease (<1%)
  - Multiply-recurrent lesions have increased risk of fibrosarcomatous transformation → ↑↑metastatic potential
- **Giant cell fibroblastoma** (pediatric variant): occurs in early childhood; affects **boys** >> girls; possesses same **COL1A1-PDGFB translocation** as DFSP; favors **head/neck**, trunk and groin; histologically resembles DFSP, but has distinctive **pseudovascular spaces surrounded by giant cells**

### Atypical fibroxanthoma (AFX)

- Relatively common low-grade, superficial (dermally based) sarcoma that arises on **chronically sun-damaged skin** (head and neck #1 > upper trunk and extremities) of **elderly** (70–80 years old); p/w **rapidly growing ulcerated red nodule**
- Recurs in up to 5% of cases, but **almost never metastasizes**
- Treatment: Mohs > WLE
- Histology: fairly well-circumscribed, **overtly malignant** dermal proliferation **slammed up** against an atrophic/

ulcerated epidermis; tumor extends down to deep dermis in a “pushing” fashion; tumor is comprised of variable mixture of **four main cell types**: spindle cells, **histiocyte-like cells**, **xanthomatous cells**, and **bizarre multinucleated giant cells**; all cell types are notable for hyperchromatic nuclei, pleomorphism, and a **high mitotic rate** w/ numerous wildly atypical mitoses (Fig. 6-37)

- **AFX never extensively infiltrates SQ fat** → if present, should call it “superficial UPS” or pleomorphic dermal sarcoma (discussed below)
- **Immunostains**: **no specific immunostain** to confirm Dx of AFX! Stains positively with **CD10** (nonspecific), **procollagen I**, **CD99**, **CD68** (histiocyte-like cells), and **SMA** in a “**tram-track**” pattern (pattern consistent with myofibroblastic differentiation, rather than true smooth muscle)
- **AFX is a diagnosis of exclusion** → must first rule out other entities in the “**SLAM**” Ddx (malignant dermal spindle cell neoplasm **SLAM**med up against the epidermis):
  - **SCC** (sarcomatoid/spindle cell variant): stains positively with high-molecular weight keratin (**CK903** and **CK5/6**), **p63** and **p40** (newest and most specific marker)
  - **Leiomyosarcoma**: **desmin+** and **SMA+** (diffuse cytoplasmic staining vs tram-track in AFX)
  - **AFX**: negative for high-molecular weight keratin, **p63**, **p40**, **S100**, **SOX10**, and **desmin**
  - **Melanoma** (spindle cell or desmoplastic variants): **S100+** and **SOX-10+**
- Lesions related to AFX:
  - **Pleomorphic dermal sarcoma (PDS)**: recently described entity; arises on same sites as AFX, but has **deeper subcutaneous invasion**, necrosis, lymphovascular or perineural invasion; a/w ↑**recurrence** (28%) and ↑↑**metastases** (10%)
    - **Clinical relevance**: if an AFX-like lesion has significant involvement of fat → would be wise to call it a PDS instead
  - **Undifferentiated pleomorphic sarcoma (UPS)**: “UPS” has replaced the old term “MFH” (malignant fibrous

histiocytoma); UPS has similar ugly cell types as AFX, but is a deep sarcoma that arises in **deep soft tissues** (high #1) of middle-aged adults; 5 year mortality = 50%

## Other fibroblastic proliferations

### Angiofibroma

- Clinical features
  - **Fibrous papule**: solitary domed papule; nose/face of adults; mimics BCC
  - **Pearly penile papules**: aggregated pearly papules glans penis
  - **Facial/periungual angiofibromas**: a/w various syndromes
- Histopathologic features
  - Dermal proliferation of stellate (triangular) or multinucleated fibroblasts with **fibrotic stroma** and ectatic thin-walled vessels
- Other high-yield facts/associations
  - Multiple facial angiofibromas: seen in **TS**, **MEN1**, and Birt-Hogg-Dubé
  - Periungual fibroma (**Koenen’s tumor**) is also characteristic of TS

### Sclerotic fibroma

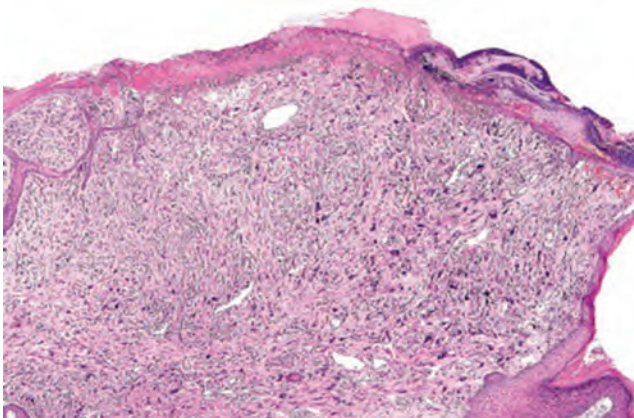
- Clinical features
  - Firm/pearly papule or nodule; any site; can be solitary or multiple
- Histopathologic features
  - Sclerotic collagen bundles arranged as intersecting stacks (“**plywood**” pattern); inconspicuous spindle cells between collagen fibers
- Other high-yield facts/associations
  - **Examination tip**: the characteristic histology and association with Cowden’s syndrome are the only two commonly tested points

### Pleomorphic fibroma

- Clinical features
  - Domed or pedunculated papules on extremities of adults; F > M; **resemble skin tags clinically**; benign
- Histopathologic features
  - Looks similar to acrochordon, but has scattered hyperchromatic, bizarre, multinucleated, or stellate cells; lacks mitoses
- Other high-yield facts/associations
  - May simply represent a skin tag with “ancient change”

### Multinucleate cell angiohistiocytoma

- Clinical features
  - Multiple, grouped red papules on **dorsal hands** or legs of women in their 40s; benign
- Histopathologic features
  - Looks like a “cell-poor DF” w/ **characteristic multinucleated giant cells** and prominent proliferation of **dilated vessels** in dermis; stains like DF (factor 13a+ and S100 negative)



**Figure 6-37.** Atypical fibroxanthoma. Low-power view of a pleomorphic, ulcerated tumor. Note the lateral collarette. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)

### Epithelioid cell histiocytoma (epithelioid fibrous histiocytoma)

- Clinical features
  - Solitary, pyogenic granuloma-appearing papules; most common on **thighs** of 50 year old **women**
- Histopathologic features
  - Well-circumscribed dermal proliferation of **epithelioid cells (resembles Spitz nevus cells)** w/ **epidermal collarette** and dermal sclerosis; stains like a DF
- Other high-yield facts/associations
  - Boards: only the histology is likely to be tested

### Acral fibrokeratoma

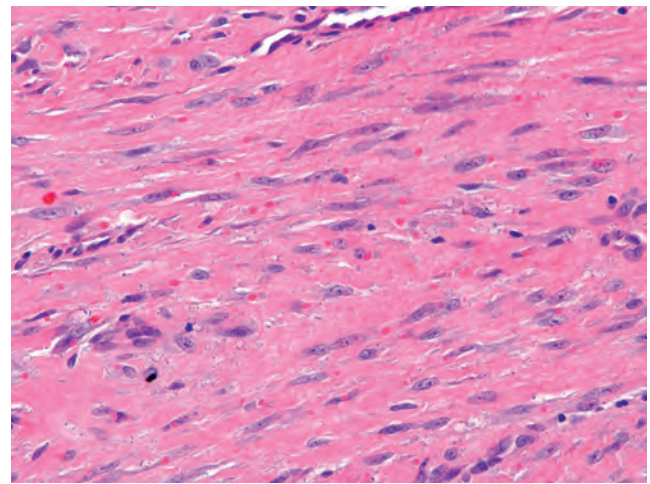
- Clinical features
  - Middle aged adults; **finger**; **exophytic keratotic papule** w/ **surrounding collarette**
- Histopathologic features
  - Hyperkeratosis/epidermal acanthosis w/ dermal collagen fibers oriented perpendicular to skin surface; **lacks nerves**
- Other high-yield facts/associations
  - DDX: **supernumerary digit** (has abundant nerve fascicles) and periungual fibroma (more vascular)

### Dermatomyofibroma

- Clinical features
  - Young adults; F > M; solitary, well-circumscribed 1–2 cm oval **plaque** resembling plaque type DFSP or DF; most commonly on **upper trunk/neck**; benign
- Histopathologic features
  - Reticular dermis has **long fascicles of spindled myofibroblasts** arrayed **parallel** to the skin surface; **respects adnexal structures** (vs ablated in DF)
- Other high-yield facts/associations
  - Derived from myofibroblasts → **SMA+** (tram-track); **CD34 negative** (distinguishes from plaque-type DFSP), **S100 negative** (distinguishes from NF), **factor 13a negative** (vs DF), and **desmin negative** (vs pilar leiomyoma)

### Inclusion body fibromatosis (infantile digital fibroma)

- Clinical features
  - **Infants**; multiple firm papules on **dorsolateral fingers and toes** (spares thumb/first toe); benign, but has **50% recurrence rate**
- Histopathologic features
  - Entire dermis filled w/ intersecting **fascicles of plump spindle cells**; on high power can see the **pathognomonic pink-red inclusion bodies** (same size as an RBC) (**Fig. 6-38**)
- Other high-yield facts/associations
  - **Pink inclusions** are **composed of actin filaments** → **SMA+**, **calponin+**, **desmin+**, and stain **red w/ trichrome**



**Figure 6-38.** Infantile digital fibromatosis. Infantile digital fibromatosis is composed of fascicles of bland spindle cells that have perinuclear intracytoplasmic eosinophilic inclusions. (Courtesy of Dr. KJ Busam.) (From Busam KJ. Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology, 2nd edn. Elsevier, 2015.)

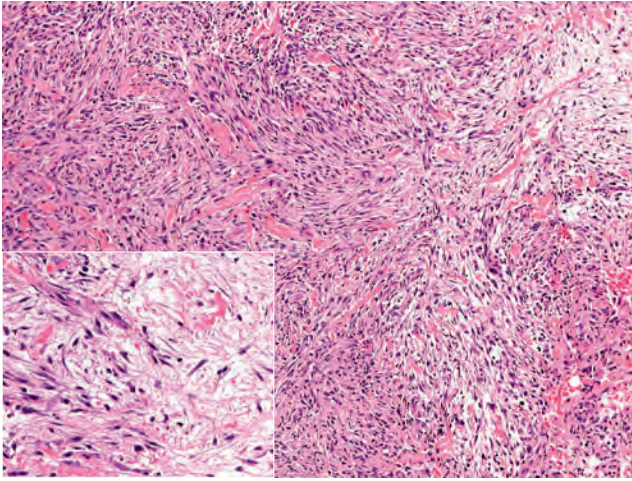
### Fibromatosis

- Clinical features
  - Superficial variants:
    - Palmar (**Dupuytren's**)
    - Plantar (**Ledderhose**)
    - Penile (**Peyronie's**)
    - Knuckle pads
  - Deep variants: seen in abdominal wall, intra- and extraabdominal → all a/w **↑morbidity and mortality**
- Histopathologic features
  - Dermal/subcutaneous **extremely long fascicles** of bland spindled, **wavy fibroblasts** and myofibroblasts; often infiltrates fascia and skeletal muscle
- Other high-yield facts/associations
  - **Deep desmoid tumors** may be a/w **Gardner's syndrome**, have **β-catenin mutations**, and stain **β-catenin+**
  - Superficial fibromatoses: benign but locally destructive → **excision + fasciotomy** is **TOC**

### Nodular fasciitis

- Clinical features
  - Young to middle aged adults; **rapidly growing** 1–5 cm subcutaneous nodule; classically on **upper extremities (#1 site overall)** and **head/neck (#1 site in children)**; may have **history of trauma**; benign self-limited lesions
- Histopathologic features
  - **Well-circumscribed**; deep **subcutaneous** nodule often a/w fascia; plump spindle cells with **"tissue culture"** appearance and **frequent mitoses** (but none atypical); admixed lymphocytic inflammation; characteristic **myxoid stroma** (early), collagenous stroma (later); numerous small blood vessels with **extravasated RBCs** (**Fig. 6-39**)
  - Prototypical **"pseudosarcoma"** because of its **↑cellularity** (comprised of spindle cells) and frequent mitoses





**Figure 6-39.** Nodular fasciitis. Proliferation of spindle-shaped and plump fibroblasts arranged in a haphazard array with focally myxoid stroma. The plump and spindle-shaped fibroblasts within the myxoid stroma have a vague “tissue culture-like” appearance. (Courtesy, Lorenzo Cerroni, MD.) (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)

- Other high-yield facts/associations
  - Boards tip: histology is frequently tested b/c it is a classic “pseudosarcoma” → potential medico-legal pitfall
  - Major clues: **myxoid stroma**, **sharp circumscription**, **lack of atypical mitoses**, and **RBC extravasation**

### Fibrous hamartoma of infancy

- Clinical features
  - Infants; M > F (3:1); skin-colored subcutaneous nodule; shoulder/arm/axilla; recurrence uncommon after excision
- Histopathologic features
  - Poorly circumscribed hamartoma; benign
  - **Triphasic proliferation**:
    - **Plump spindle cells in fascicles** a/w collagenous stroma
    - Small aggregates of **immature mesenchymal cells**
    - **Mature fat**
- Other high-yield facts/associations
  - Frequently tested on dermpath specialty boards

### Myofibroma (infantile myofibromatosis)

- Clinical features
  - **Infantile form**: 50% at birth; p/w **multiple** pink-violaceous dermal/SQ nodules **head** (>trunk); F > M; can involve bones and internal organs → ↑**morbidity and mortality**
  - **Adult form**: **solitary** 1–3 cm nodules; most commonly on **head/neck**; **benign**
- Histopathologic features
  - **Biphasic proliferation**:
    - **Hypocellular areas** of blue-pink nodules (may appear cartilaginous, “myoid,” or hyalinized) w/ fascicles of bland myofibroblasts
    - **Hypercellular areas** w/ primitive-appearing round, blue cells with ↑N:C ratio, and ectatic **staghorn** (“hemangiopericytoma-like”) vessels



**Figure 6-40.** Collagenomas. Periumbilical skin-colored papulonodules. (From Zeller S, Marx SJ. *J Amer Acad of Dermatol* 2009;61:2:319–322)

- Stains confirm myofibroblastic derivation (**SMA+** **tram track** and **desmin negative**)
- Other high-yield facts/associations
  - Most common form of fibromatosis in children
  - If limited to soft tissue and bone involvement → self-resolves; good prognosis
  - **Visceral involvement** is a/w **high mortality**
  - Variant: when hypercellular areas predominate → termed **infantile hemangiopericytoma**

### Giant cell tumor of tendon sheath (Tenosynovial giant cell tumor)

- Clinical features
  - Adults; F > M; firm subcutaneous nodule; most common on **fingers**; benign, but 30% recur
- Histopathologic features
  - Nodular proliferation of round polygonal cells and **osteoclastic giant cells**; variable collagen, inflammation and hemosiderin in the background
- Other high-yield facts/associations
  - **Boards tip**: this is the only testable neoplasm w/ numerous osteoclastic giant cells

### Connective tissue nevus (collagenoma and elastoma)

- Clinical features
  - Firm papulonodules or plaque; any site
- Histopathologic features
  - **Collagenoma**: haphazard, thickened collagen bundles
  - **Elastoma**: ↑elastic fibers; histologic changes may be very subtle → need VVG stain
- Other high-yield facts/associations
  - **Syndromes a/w connective tissue nevi**:
    - **TS**: Shagreen patch; pebbly plaque on the lower back
    - **MEN-1**: pedunculated collagenomas (**Fig. 6-40**) + facial angiofibromas + endocrine neoplasia
    - **Buschke-Ollendorf** (aka dermatofibrosis lenticularis disseminata): either collagenomas or elastomas + **osteopoikilosis**
    - **Proteus syndrome**: cerebriform plantar connective tissue nevi



## 6.11 VASCULAR PROLIFERATIONS

- As a general rule, benign vascular lesions:
  - Have: **lobular growth patterns** (multiple lobules/nodules of vessels) and **well-circumscribed** borders
  - May have: mitoses (but lack atypical mitoses) and reactive atypia (enlarged/"revved-up" endothelial cells)
  - Do not have: infiltrative architecture, hyperchromatic nuclei, markedly pleomorphic cells, atypical mitoses, or necrosis

### Benign vascular lesions

#### Vascular malformation (includes "port wine stain", "cavernous hemangioma" old terminology)

- Present **at birth**; may be capillary, venous, lymphatic, or arteriovenous malformation → **does not rapidly enlarge** (because it is a malformation rather than a true neoplasm), unlike infantile hemangiomas
- Variable clinical appearances; tend to persist and become more verrucous over time
- **GLUT-1 negative**
- Associations: **Maffucci syndrome**, **Klippel-Trenaunay**, **Sturge-Weber**, **Blue Rubber Bleb** (cavernous hemangiomas), **Kasabach-Merritt syndrome**, and **Proteus syndrome**

#### Intravascular papillary endothelial hyperplasia (Masson's tumor, pseudoangiosarcoma)

- **Reactive phenomenon** (organization of a thrombus) most commonly seen **within a vein** (> in a vascular malformation/neoplasm > extravascular hematoma)
- **Slow-growing dusky nodules**; most commonly in veins of **head/neck** or fingers
- Histology: thrombosed vessel with **intraluminal proliferation of endothelial cells** → forms **papillary structures** mimicking angiosarcoma
  - **Major clues** = **sharply circumscribed** (entirely contained within the thrombosed vessel), lacks multilayering of endothelial cells, and cells are not hyperchromatic

### Angiokeratoma

- Superficial keratotic/verrucous vascular lesions
- Five types:
  - Angiokeratoma of Mibelli: 10–15 years old; fingers and toes
  - Angiokeratoma of Fordyce: older men (scrotum) or females (vulva)
  - Angiokeratoma corporis diffusum: multiple lesions in childhood/adolescence; bathing suit distribution; seen in **Fabry disease** and other enzyme deficiencies

- Angiokeratoma circumscriptum (AC): children; F > M; aggregate of lesions forming a plaque
- Solitary and multiple angiokeratomas: children and adults; arise on any site; may be related to chronic irritation/trauma of superficial dermal vessel
- Histology: dilated superficial dermal vessels with epidermal hyperplasia; rete hug vessels

### Infantile hemangioma

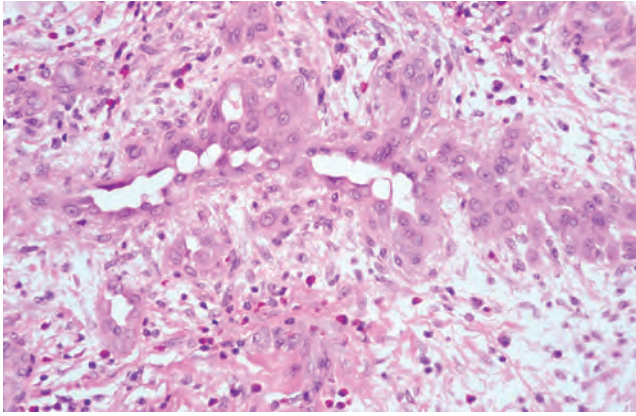
- Onset in first couple months of life (usually not obvious at birth) → **rapid growth for 4 to 6 months** → **slow involution** over years
  - Standard teaching – 50% involute by 5 years and 90% by 9 years
- ↑incidence in: **premature infants, females and placental abnormalities**
- Most are superficial and therefore clinically bright red; arise at any site
  - Deeper lesions are purple-blue
- Histology: dense dermal +/- subcutaneous **capillary proliferation** that is **GLUT-1 positive**
- Treatment for problematic lesions (ulceration, sensitive location): **β-blockers** (first line), corticosteroids, and surgical or laser therapies
  - **Airway hemangioma**: concern for involvement if a plaque-type hemangioma is present from the preauricular cheek along the mandible, lower lip, chin, or anterior neck (**beard distribution**)
  - **Periorbital hemangioma**: concern for development of astigmatism (from direct pressure on the globe) and amblyopia (caused by obstruction of the visual axis)
- Rapidly involuting infantile hemangioma (**RICH**): fully developed at birth, no postnatal proliferation, and involutes over 1 year; **GLUT-1 negative**
- Noninvoluting infantile hemangioma (**NICH**): fully developed at birth, grows proportionally with patient; does not involute; **GLUT-1 negative**

### Pyogenic granuloma (lobular capillary hemangioma)

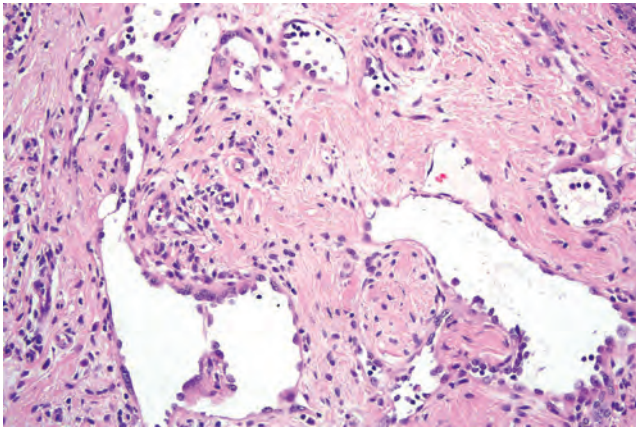
- Benign capillary proliferation; a/w **trauma, pregnancy**, and medications (**OCPs, oral retinoids, indinavir**, and **EGFR-inhibitors**)
- Most common in children and young adults; rapidly growing, exophytic, and **hemorrhagic papule w/ epidermal collarette**
- Common sites: **gingiva (pregnancy)**/oral cavity, lips, and digits
- Histology: **well-circumscribed, lobular** proliferation of small capillaries w/ RBC extravasation; ↑mitotic activity (no atypical mitoses) and reactive atypia of endothelial cells

### Epithelioid hemangioma (ALHE, angiolymphoid hyperplasia with eosinophils)

- Grouped nodules or plaques on head/neck (most commonly **around ear**) of young to middle-aged adults



**Figure 6-41.** Angiolymphoid hyperplasia with eosinophils. The vascular channels are lined by plump, partly vacuolated endothelial cells. There are scattered eosinophils in the stroma. (H&E) (From Weedon D. *Weedon's Skin Pathology*, 3rd edn. Elsevier, 2009.)

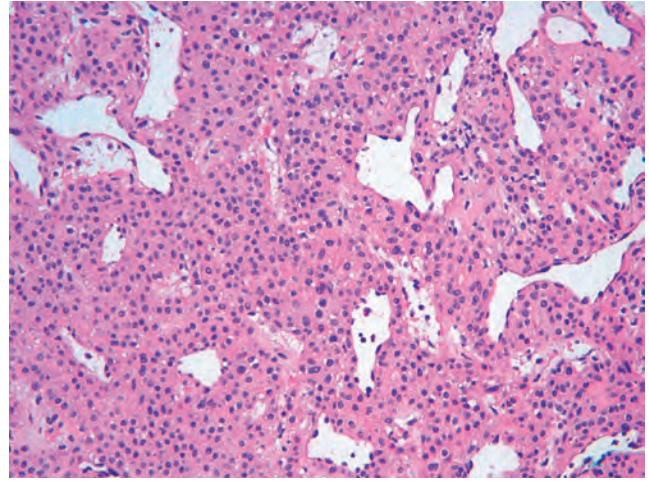


**Figure 6-42.** Hobnail hemangioma: the endothelial cells are prominent and protrude into the lumen. Note the papillary processes. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th edn. Elsevier, 2011.)

- Histology: lobular dermal proliferation of capillaries and larger, thicker vessels w/large epithelioid endothelial cells lining the vessel lumen; intracytoplasmic vacuoles within endothelial cells (represents primitive vascular lumens); background of lymphocytic and eosinophilic inflammation (often intense, with occasional lymphoid follicles); fibrotic stroma (Fig. 6-41)

### Hobnail hemangioma (targetoid hemosiderotic hemangioma)

- Clinically distinctive, acquired lesion; affects children and young adults; legs (> arms > trunk); red-brown papules with "target-like" appearance (dark centrally → pale area is first ring → bruise-like patch in outer ring); possibly a/w trauma
- Histology: biphasic lesion
  - Upper dermis (boards favorite): markedly dilated thin-walled vessels lined by thin, elongated endothelial cells that protrude ("hobnail") into lumen (Fig. 6-42)
  - Lower dermis: vessels become more slit-like; RBC extravasation and hemosiderin deposition within dermis



**Figure 6-43.** Glomus tumor. Cytologically bland round tumor cells with uniform nuclei and sharp cellular membranes surround blood vessels. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015.)

### Tufted angioma

- Pink-red macules, plaques located on neck or trunk → spreads to involve large areas
- Most commonly appears in first year of life (25% congenital); congenital form can be a/w Kasabach-Merritt phenomenon
- Histology: dermal/subcutaneous tightly packed lobules of capillaries in a "cannonball" pattern; a characteristic empty-appearing "crescent" surrounds the periphery of each lobule (represents dilated lymphatic channels)

### Glomeruloid hemangioma

- Rare vascular proliferation seen in POEMS syndrome (> multicentric Castelman's disease); most common on trunk/proximal extremities; does not clinically appear different than common cherry angiomas
- a/w ↑VEGF levels → vascular proliferation
- Histology (boards favorite): well-circumscribed dermal proliferation comprised of dilated vessels that are filled centrally with a small ball of well-formed capillary loops → resultant architecture resembles renal glomeruli

### Glomus tumor/glomangioma

- Benign proliferations of perivascular epithelioid cells derived from Suquet-Hoyer canal
- Glomus tumor (more common):
  - Solitary; painful; favors young adults; subungual (most common site)
  - Histology: dense proliferation of glomus cells surrounding small vascular spaces (Fig. 6-43)
- Glomangioma/glomulovenous malformation (less common):
  - Arises in infancy or childhood; frequently multiple lesions, not painful
  - Histology: main feature is large, dilated vessels surrounded by a smaller number of glomus cells
- Treatment: surgery is curative



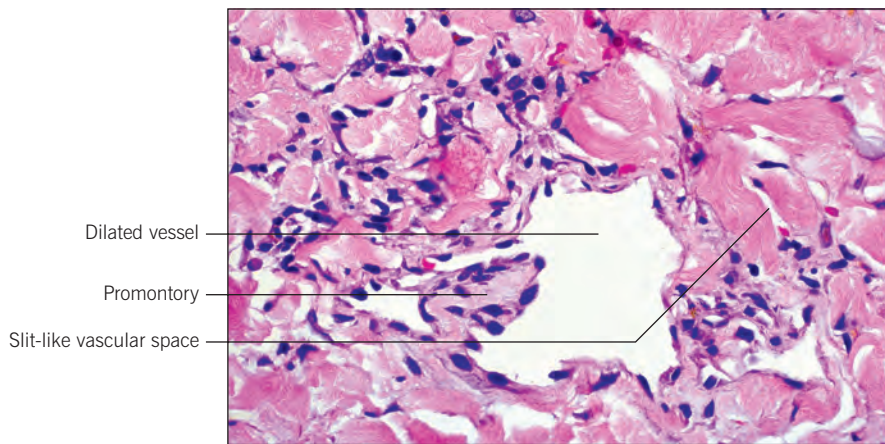


Figure 6-44. Kaposi sarcoma (medium mag). (From Rapini R. *Practical Dermatopathology*, 2nd edn. Elsevier, 2012.)

## Borderline vascular neoplasms

### Kaposiform hemangioendothelioma

- Rare vascular tumor of childhood; a/w **Kasabach-Merritt** phenomenon; **GLUT-1 negative**
- Violaceous plaque; becomes massively engorged when Kasabach-Merritt occurs
  - Usually involves an extremity
  - Can be present in retroperitoneum and present as ecchymoses
- Histology: nodules of densely packed spindle cells with slit-like lumens (resembles nodular Kaposi sarcoma)
  - Positive for CD34 and CD31, and is factor VIII negative

### Kaposi sarcoma

- HHV-8 (present in 100%) induced vascular proliferation w/ variable clinical behavior
- Clinical variants:
  - **Classic KS: Mediterranean**, Ashkenazi Jewish descent; **elderly males**; initial lesions on **distal extremities** → some progress to disseminated involvement
  - **African endemic**: **young African males** in endemic regions; lymph node involvement and **fulminant/fatal course**
  - **Iatrogenically immunocompromised**: seen in patients with organ transplants, cancer, and autoimmune diseases
  - **AIDS-associated**: most common in **homosexual males**; solitary (trunk and **midface** common) or multiple lesions; may disseminate
- Slowly growing violaceous patches, plaques, or nodules
- Histology:
  - **Patch stage**: subtle infiltrative small vessels with bland endothelium and associated **plasma cells**; **RBC extravasation + hemosiderin +/- promontory sign** (Fig. 6-44)
  - **Plaque stage**: proliferation more pronounced and extends deeper into dermis/subcutis with plasma cells
  - **Nodular stage**: cellular nodules of plump spindle cells with slit-like lumina containing red blood cells (**sieve-like appearance**); **cells are never as atypical as those seen in angiosarcoma**; may have more ectatic vessels in the periphery; plasma cells

- Immunohistochemistry: nuclear positivity for latency-associated nuclear antigen (**LANA-1**) of HHV-8 is very helpful diagnostically (~100% sensitive and specific)
- Treatment: cryotherapy, laser surgery, PDT, topical alitretinoin gel, and radiation therapy
  - Rapidly progressive KS w/ visceral involvement is treated w/ systemic chemotherapy

### Other borderline vascular neoplasms (rare; not commonly tested)

- Dabska-type hemangioendothelioma, retiform hemangioendothelioma (architecture resembles rete testes), and epithelioid hemangioendothelioma

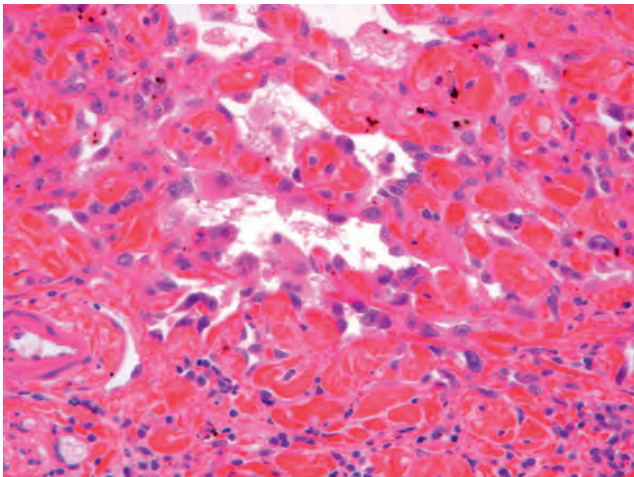
## High-grade malignant vascular neoplasms

### Angiosarcoma

- Cutaneous angiosarcoma seen in a variety of clinical settings:
  - **Elderly, sun-damaged sites (head/neck #1)** (Fig. 6-45)
  - **Stewart-Treves syndrome**: chronic lymphedema associated (mostly following breast cancer treatment with axillary lymph node dissection)
  - **Postradiation**: most commonly on breast, arises after radiation therapy for breast cancer
- Histology: large, **hyperchromatic, pleomorphic** tumor cells **dissecting between collagen bundles** → forms **anastomosing vascular networks**; endothelial cells lining the vessels have "**multilayered**" or "**piled-on**" **architecture** (many malignant endothelial cells crowded on top of each other with some tumor cells floating freely inside the lumen → this is never seen in benign vascular neoplasms!); prominent **hemorrhage** (Fig. 6-46)
  - Poorly differentiated areas may have large epithelioid cells which resemble carcinoma and lack clear vascular differentiation
  - Immunostains: **CD31+**, **CD34+**, **ERG+** (most sensitive and specific), and **FLI-1+**



**Figure 6-45.** Dark blue-purple plaques and nodules of angiosarcoma on the forehead and scalp of a 70-year-old man. The circular area is the biopsy site. (From Callen JP, et al. *Dermatological Signs of Internal Disease* 4th edn. Elsevier, 2009.)



**Figure 6-46.** Angiosarcoma histopathology. Anastomosing dilated vessels, lined by crowded endothelial cells, extend between preexisting collagen bundles. (H&E-saffron stain; original magnification: 40x) (From Karkouche R, Kerob D. *J Amer Acad Dermatol* 2013;69:3e142–e143)

- Poor prognosis
- Treatment: surgical excision with wide margins, radiation therapy
- **Boards fodder:** c-MYC amplifications (detected by immunostaining or FISH) reliably distinguishes between atypical vascular lesions (“AVLs,” which are negative) and radiation-induced angiosarcoma (positive)

## Vascular neoplasm associations

See Fig. 6-47.

## 6.12 NEOPLASMS OF ADIPOCYTIC LINEAGE

### Lipoma

- Benign neoplasm composed of mature adipose tissue; subset with heterogeneous clonal aberrations involving the chr 12q13-15 region
- Soft subcutaneous nodule; any anatomic site; typically middle-aged adults
- Histology: well-circumscribed sheets of mature adipocytes w/ minimal to no increase in fibrous tissue
- **Conditions a/w multiple lipomas:**
  - Familial multiple lipomatosis
  - Madelung’s disease
  - Gardner syndrome
  - Bannayan-Riley-Ruvalcaba syndrome
  - Proteus syndrome
  - CLOVES syndrome
  - PTEN hamartoma tumor syndrome

### Angiolipoma

- Young adults; forearms (#1); often multiple lesions; **painful**
- Small subcutaneous nodules
- Histology: mature fat with areas containing **proliferative capillary lobules** that are characteristically **thrombosed** (→ hence painful) (Fig. 6-48)
- Benign; excision is curative

### Spindle cell/pleomorphic lipoma

- Firm, subcutaneous nodule on **posterior neck/shoulder** of adult **males**
- Histology: mature fat, areas of bland spindle cells with a **myxoid background** and characteristic **thick “ropey” collagen fibers** (Fig. 6-49)
  - Pleomorphic lipoma: identical, except it additionally has large **“floret-like” cells** (Fig. 6-50)
- Spindle cells are **CD34 positive**
- Benign; excision is curative

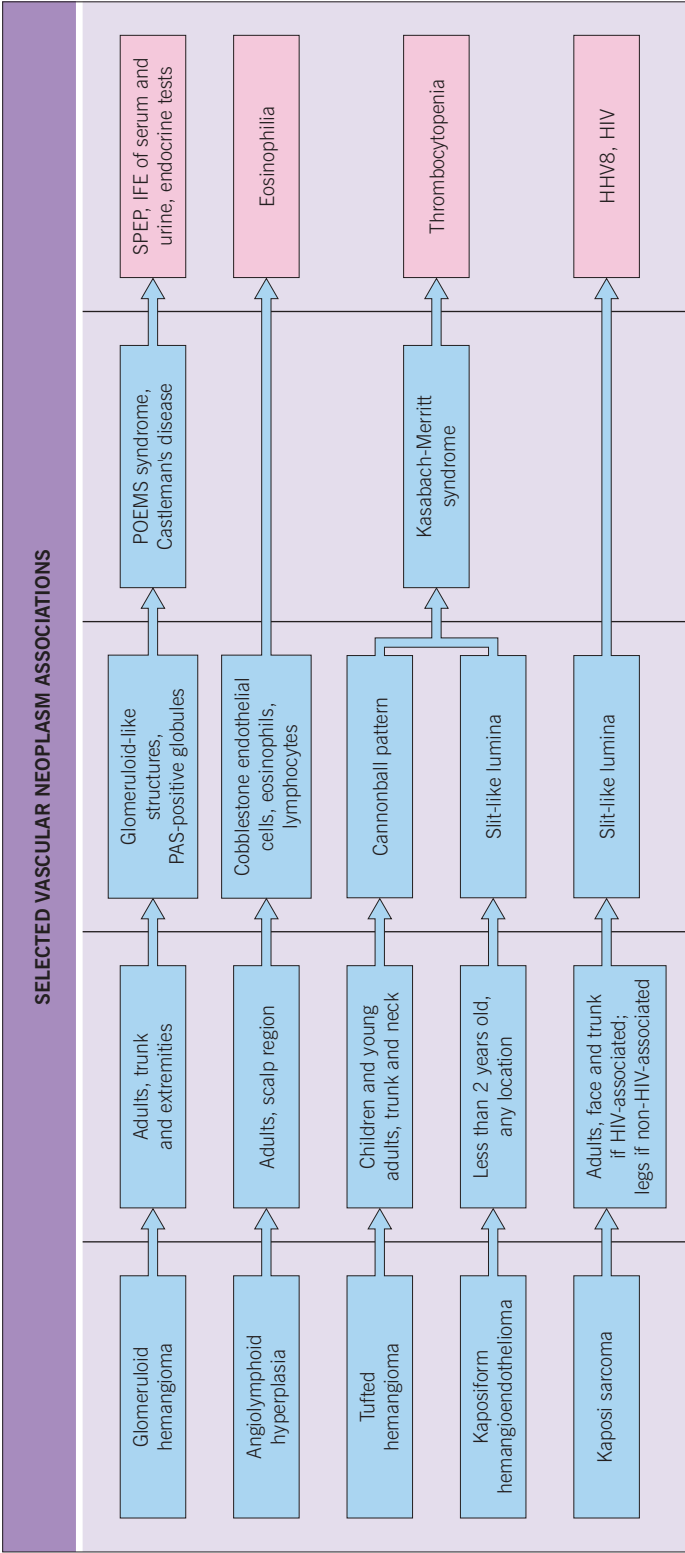
### Hibernoma

- Benign tumors of **brown fat**
- **Young adults;** trunk and neck; slowly growing subcutaneous nodules
- Histology: hibernoma cells (polygonal cells with **eosinophilic, multivacuolated cytoplasm**) admixed with normal appearing adipocytes
- Benign; excision is curative
- **Boards tip:** only the histology is likely to be tested

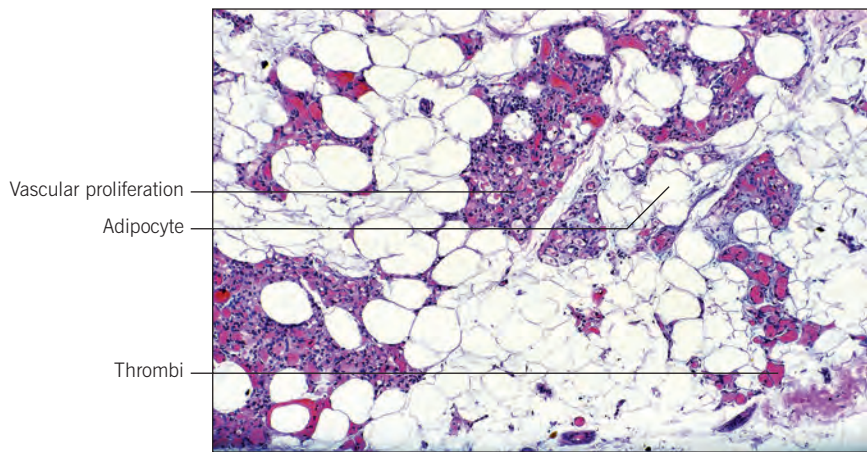
### Well-differentiated liposarcoma (atypical lipomatous tumor)

- Uncommon in the skin; typically involves deep soft tissue or retroperitoneum; large lesions that slowly enlarge
- **MDM2 amplification (>99%)** → extremely sensitive and specific tool

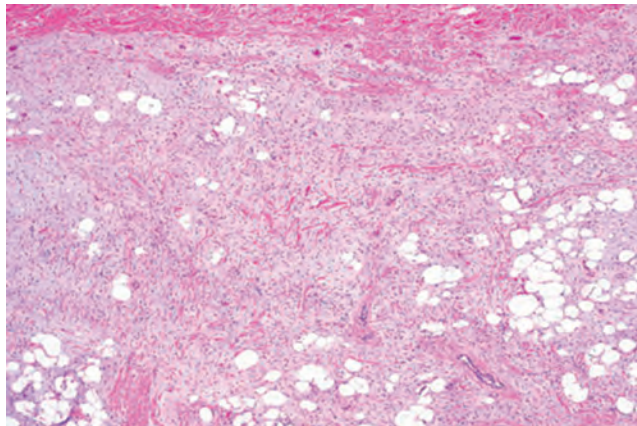




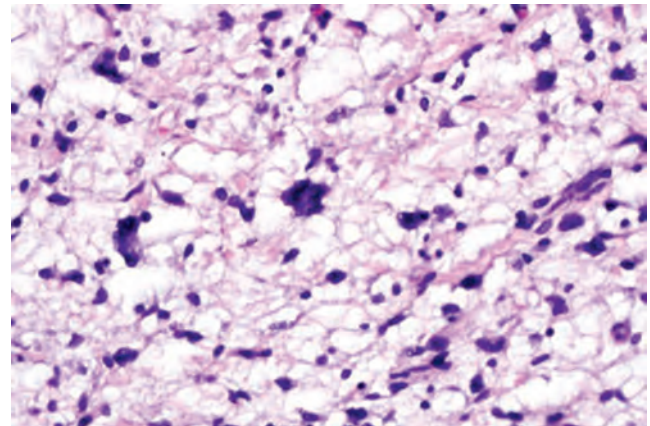
**Figure 6-47.** Selected vascular neoplasm associations. IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis; HHV8, human herpesvirus 8; HIV, human immunodeficiency virus; PAS, periodic acid-Schiff stain. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



**Figure 6-48.** Angiolipoma (From Rapini R. *Practical Dermatopathology*, 1st edn. Elsevier, 2012.)



**Figure 6-49.** Spindle cell lipoma. Low-power view of an encapsulated tumor composed of spindled cells with admixed foci of adipocytes. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)



**Figure 6-50.** Pleomorphic lipoma. High-power view of floret giant cells. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*, 1st edn. Elsevier, 2011.)

- Histology: mixture of mature fat and **fibrous bands containing hyperchromatic atypical stromal cells** (most important finding); **lipoblasts** may be seen but are not essential for diagnosis
- Prone to local recurrence; dedifferentiation to a high-grade sarcoma can also occur

### Myxoid/round cell liposarcoma

- Rare type of liposarcoma; most testable point is its characteristic histology (buzzword: “chicken-wire” vessels)

## 6.13 DERMOSCOPY

- Synonyms: dermatoscopy, epiluminescence microscopy, skin surface microscopy, and magnified oil immersion diascopy
- An in vivo, noninvasive technique to enhance the color and structure of the epidermis, DEJ and superficial dermis → reveals features that cannot be seen with the naked eye
- May enhance diagnostic accuracy
- Helps distinguish melanocytic from nonmelanocytic lesions

- Dermoscopy colors of keratinizing, melanocytic, and vascular tumors (see Fig. 6-51)








### Dermoscopic features of nonmelanocytic lesions (see Table 6-8 and Figs. 6-52 through 6-59)

#### Seborrheic keratosis

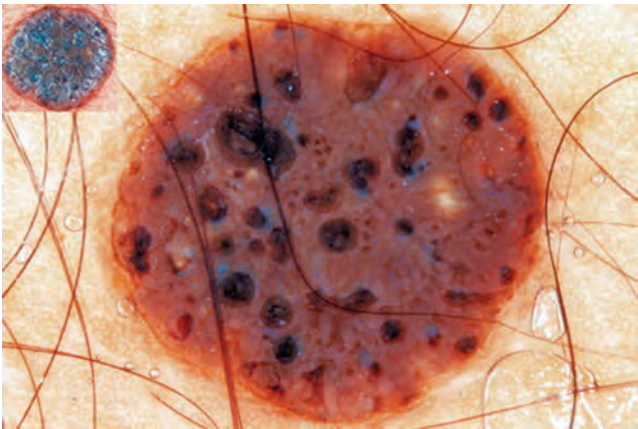
- Milia-like cysts
- Comedo-like openings
- Fissures and ridges
- Moth-eaten borders
- Sharp demarcation
- Fingerprint-like pattern

#### Basal cell carcinoma

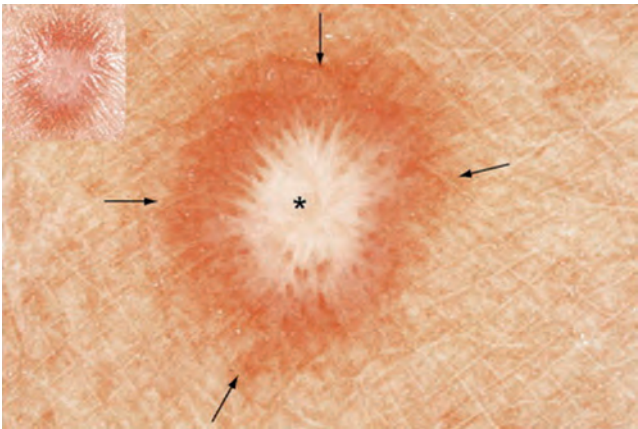
- Leaf-like structures on periphery
- Blue-gray ovoid nests and globules
- Pigmented specks
- Spoke-wheel structures
- Arborizing (branch-like) telangiectasias
- Ulceration/erosion

	<b>Orange</b>	keratin	epidermis
	<b>Yellow</b>	keratin - cholesterol	epidermis - dermis
	<b>Black</b>	melanin	stratum corneum
	<b>Brown</b>	melanin	basal layer
	<b>Gray</b>	melanin	papillary dermis
	<b>White</b>	fibrosis	dermis
	<b>Blue</b>	melanin	papillary and reticular dermis
	<b>Red</b>	hemoglobin	papillary dermis
	<b>Purple</b>	hemoglobin	reticular dermis

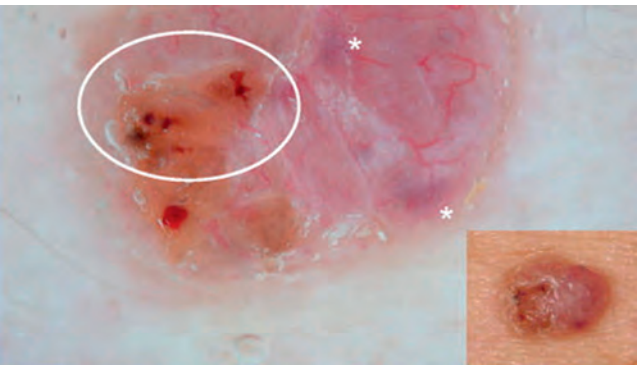
**Figure 6-51.** Dermoscopy colors of keratinizing, melanocytic, and vascular tumors. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



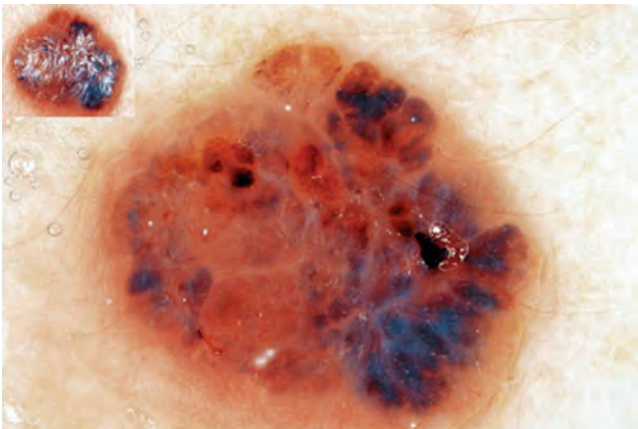
**Figure 6-52.** Seborrheic keratosis: milia-like cysts (white dots) and comedo-like openings (black targetoid circles). (From Soyer P et al. *Dermoscopy*, 2nd edn. Elsevier, 2012.)



**Figure 6-53.** Dermatofibroma: central white patch (asterisk) and subtle pigment network (arrows). (From Soyer P et al. *Dermoscopy*, 2nd edn. Elsevier, 2012)

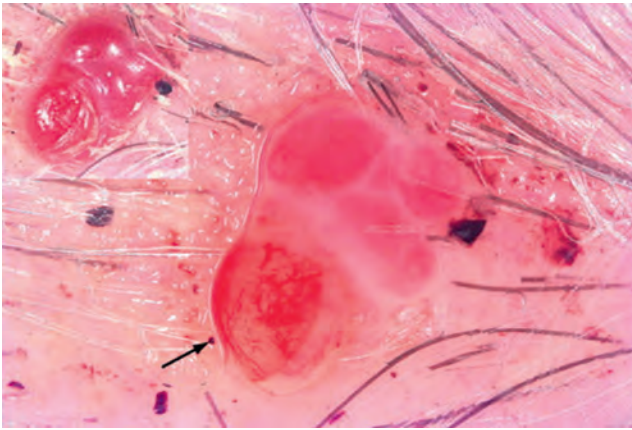


**Figure 6-54.** Basal cell carcinoma: arborizing blood vessels, blue-gray blotches (asterisks), and ulceration (circle). (From Soyer P et al. *Dermoscopy*, 2nd edn. Elsevier, 2012)

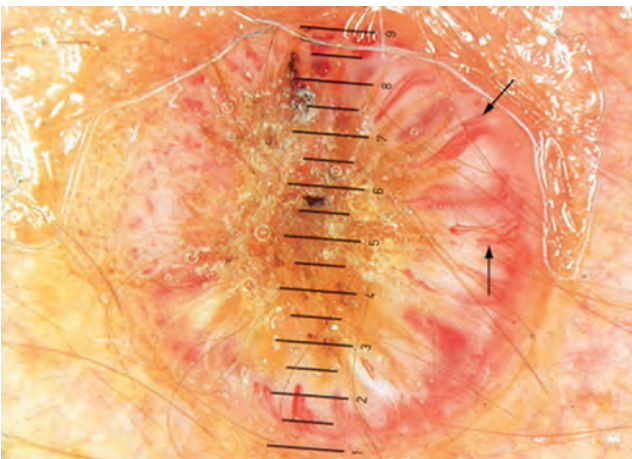


**Figure 6-55.** Basal cell carcinoma: Leaf like areas (3 o'clock to 6 o'clock at the periphery of the lesion). (From Soyer P et al. *Dermoscopy*, 2nd edn. Elsevier, 2012)





**Figure 6-56.** Pyogenic granuloma: homogenous red color with red lacunae. (From Soyer P et al. Dermoscopy, 2nd edn. Elsevier, 2012.)



**Figure 6-57.** Keratoacanthoma: classic hairpin-shaped vessels (arrows), white background (hyperkeratosis of keratinizing tumor), and central crust. (From Soyer P et al. Dermoscopy, 2nd edn. Elsevier, 2012.)

### Squamous cell carcinoma in situ

- Atypical clusters of glomerulus-like (coiled) vessels

### Squamous cell carcinoma

- Ulceration may be seen
- May be pink vs white with possible central crust/scale
- Varied-appearing blood vessels

### Dermatofibroma

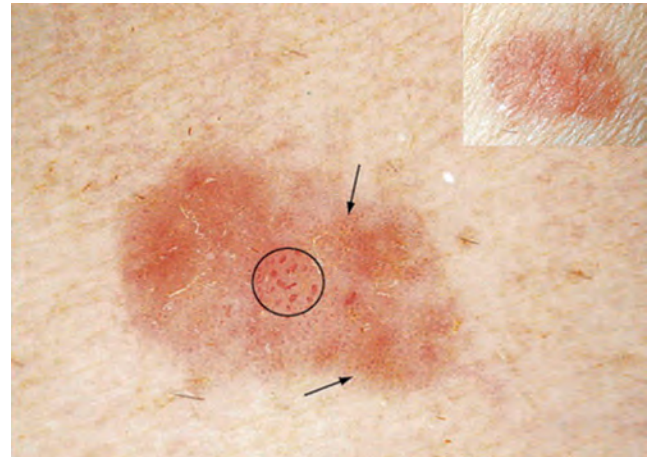
- Central white patch
- Annular (peripheral) pigment network

### Ink spot lentigo

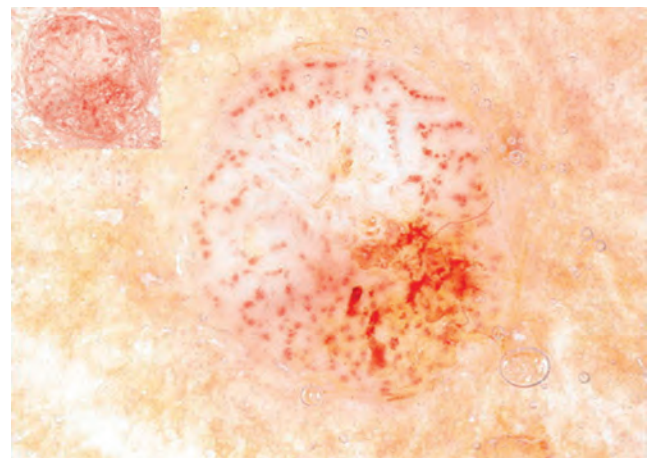
- Dark, bizarre, and sharply demarcated pigment network

### Vascular lesions (e.g., cherry angiomas)

- Red or purple lacunae



**Figure 6-58.** Pigmented Bowen's disease: well-circumscribed glomeruloid blood vessels (circle) with closely packed tiny brown dots (arrows). (From Soyer P et al. Dermoscopy, 2nd edn. Elsevier, 2012.)



**Figure 6-59.** Clear cell acanthoma: this pattern of dotted vessels is rather typical for clear cell acanthoma. (From Soyer P et al. Dermoscopy, 2nd edn. Elsevier 2012.)

### Hemorrhage

- Peripheral red/purple/blue globules

### Porokeratosis

- Cornoid lamella around lesion (seen better w/ marker applied to lesion, then wiped off with ETOH)

### Sebaceous hyperplasia

- Yellow lobules in a polygonal pattern around a central follicular opening
- Uniform, regular telangiectasia

### Dermoscopic patterns of melanocytic lesions

See Tables 6-7 through 6-9, and Figs. 6-60 through 6-65.



**Table 6-7.** Melanocytic Global Patterns

Global Pattern/Local Variant	Morphology	Histology	Diagnosis
<b>Reticular</b>	Grid of honeycomb-like line segments of black, brown, and gray covering most parts of a lesion	Elongated, pigmented rete ridges	Melanocytic lesion
Atypical pigment network	Thickened and branched line segments distributed irregularly throughout the lesion	Irregular and broadened rete ridges	Melanoma
Typical pigment network	Thin, regularly meshed and evenly spaced segments	Regular and elongated rete ridges	Benign nevus
<b>Globular</b>	Variably sized, round to oval structures covering most parts of a lesion	Aggregates of melanin-containing structures located throughout the epidermis and upper dermis	Melanocytic lesion
Irregular dots and globules	Irregular distribution of variously sized round to oval structures	Irregularly distributed melanin-containing structures in the epidermis and upper dermis	Melanoma
Regular dots and globules	Regular distribution of variously sized round to oval structures	Regularly distributed melanin-containing structures in the epidermis and upper dermis	Benign nevus
<b>Homogenous</b>	Diffuse, uniform, and structureless color in the absence of other local criteria	Varies depending on colors	Melanocytic lesion
Irregular blotches	Diffuse hyperpigmentation that varies in size and shape with irregular borders; obscures other dermoscopic features	Histopathologic structures with pronounced melanin throughout the epidermis and upper dermis	Melanoma
Regular blotches	Diffuse hyperpigmentation with uniform shape and color symmetrically located in the lesion	Histopathologic structures with pronounced melanin throughout the epidermis and upper dermis	Benign nevus
Blue-whitish veil	Irregular, confluent, and gray-blue to white-blue pigmentation	Acanthosis; hypergranulosis above pigmentation in dermis	Melanoma
Regression	Bone white scar-like depigmentation with or without gray pepper-like granules	Thickened papillary dermis with fibrosis and variable amounts of melanophages	Melanoma
<b>Starburst</b>	Pigmented streaks, and/or dots, and globules in a radial arrangement at the periphery of a melanocytic lesion	Fascicles of pigmented cells running parallel to the epidermis at the dermoepidermal junction	Melanocytic lesion
Regular streaks	Pigmented linear structures of variable thickness found regularly dispersed around the periphery of the entire circumference of a lesion	Fascicles of pigmented cells regularly dispersed running parallel to the epidermis	Reed nevus/Spitz nevus
Irregular streaks	Pigmented linear structures found irregularly dispersed around the periphery of a portion of a lesion	Fascicles of pigmented cells irregularly dispersed running parallel to the epidermis	Melanoma

**Table 6-8.** Vascular Structures Seen in Various Skin Tumors

Pattern	Definition	Diagnostic Significance
Comma	Coarse vessels that are slightly curved and barely branching	Congenital and dermal nevi
Dotted	Tin red dots densely aligned next to each other	Melanocytic lesion (often Spitz nevus and melanoma)
Linear-irregular	Linear, irregularly shaped, sized and distributed red structures	Melanoma
Hairpin	Vascular loops sometimes twisted and bending that can be surrounded by a whitish halo	With white halo: keratinizing proliferation (seborrheic keratosis, squamous cell carcinoma, keratoacanthoma, and viral wart) Without white halo: melanoma
Glomerular	Variation on the theme of dotted vessels; tortuous capillaries, often distributed in clusters mimicking the glomerular apparatus of the kidney	Bowen's disease
Arborizing	Stem vessels of large diameter branching irregularly into finest terminal capillaries; bright red color, sharply focused in dermoscopic images as a result of their location immediately beneath the surface of the tumor	Basal cell carcinoma
Crown	Groups of orderly bending, scarcely branching, vessels located along the border of the lesion	Sebaceous hyperplasia
Strawberry	Pink to red "pseudonetwork" around hair follicles of the face, frequently intermingled with fine, linear-wavy vessels; often hair follicles are filled with yellowish keratotic plugs	Actinic keratosis
Corkscrew	Linear vessels twisted along a central axis	Thick melanoma or melanoma metastasis
Milky-red color	Globules and/or larger areas of fuzzy or unfocused milky-red color often corresponding to an elevated part of the lesion	Melanoma
Polymorphous	Any combination of two or more different types of vascular structures. The most frequent is linear to-irregular and dotted vessels	Malignant tumor (melanoma, basal cell carcinoma, and squamous cell carcinoma)

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 6-9.** Site Specific Melanoma-Specific Criteria

Site	Criteria	Morphology
<b>Face, nose, ears</b>	Annular-granular structures	Brown or blue-gray dots surrounding follicular ostia
	Asymmetrically pigmented follicles	Gray circles/rings of pigment asymmetrically distributed around follicular ostia ("circle within a circle" is a variant)
	Rhomboidal structures	Thickened areas of pigmentation surrounding the follicular ostia with a rhomboidal appearance
	Gray pseudonetwork	Confluent annular-granular structures forming gray pigment surrounding follicular ostia
<b>Acral sites</b>	Parallel ridge	Parallel pigmented lines thicker than nonpigmented ones with white dots running along like a string of pearls

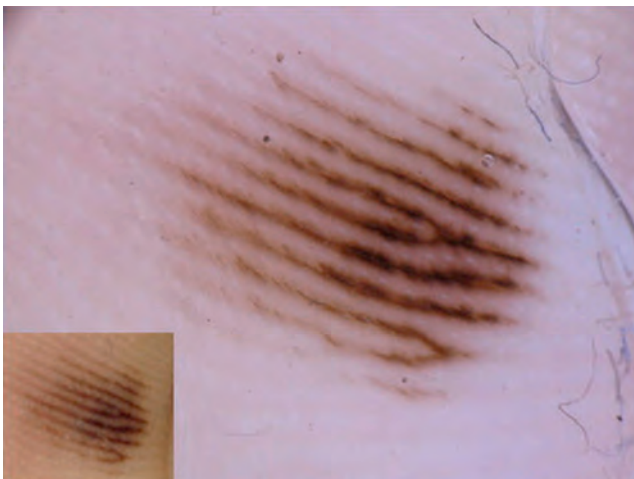
(Modified from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier, 2012)



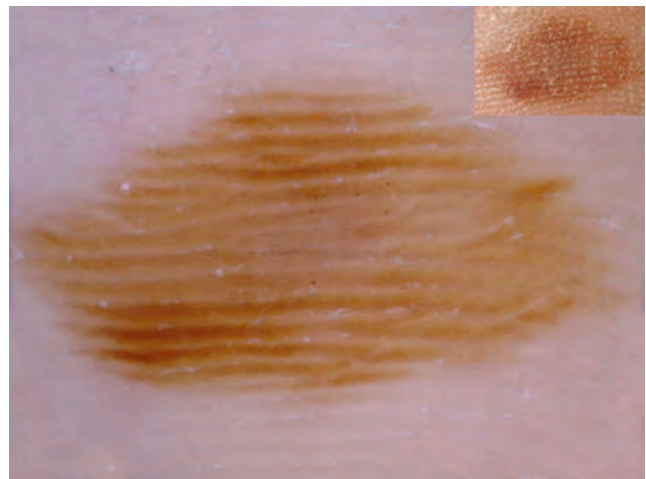
**Figure 6-60.** Typical acquired nevus with reticular pattern in dermoscopy (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



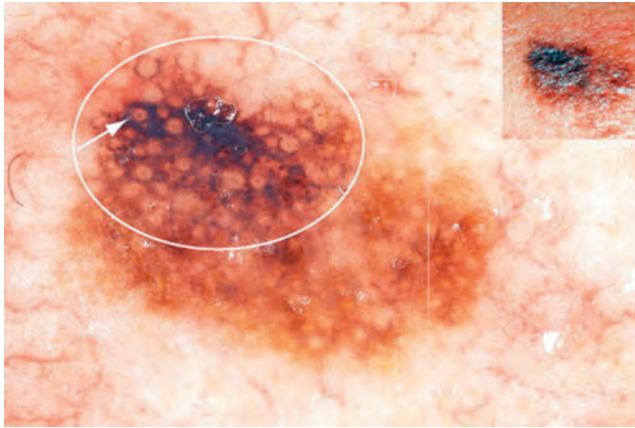
**Figure 6-61.** Reed nevus typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule). (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd edn. Elsevier, 2012.)



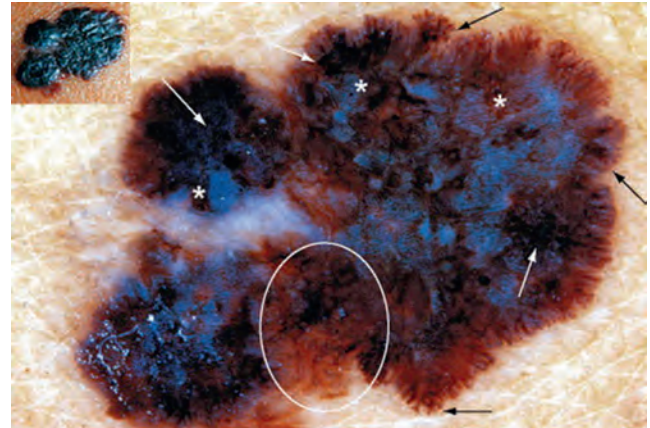
**Figure 6-62.** Acral nevus: parallel furrow pattern.



**Figure 6-63.** Acral melanoma: parallel ridge pattern.



**Figure 6-64.** Melanoma: annular-granular structures make up rhomboidal structures (arrow). Confluent rhomboidal structures make up the gray pseudonetwork (circle).



**Figure 6-65.** Melanoma: atypical pigment network (circle), irregular dots and globules (asterisks), irregular streaks (black arrows), irregular blotches (white arrows), with blue-white structures centrally.

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# 7

## Dermatopathology

Rahul Chavan and John R. Griffin

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- 7.1 ESSENTIAL CONCEPTS IN DERMATOPATHOLOGY
- 7.2 HIGH-YIELD DERMATOPATHOLOGY DIAGNOSES AT A GLANCE
- 7.3 HIGH-YIELD DERMATOPATHOLOGY DIFFERENTIAL DIAGNOSES

### 7.1 ESSENTIAL CONCEPTS IN DERMATOPATHOLOGY

Text continued on p. 376

**Table 7-1.** Features of Normal Skin

Site	Histologic Clues	Comments
Anogenital skin	<b>Undulating epidermis (papillomatous)</b> , abundant <b>smooth muscle</b> in dermis, and highly vascular	–
Areola	<b>Smooth muscle</b> (abundant); may also see lactiferous/mammary <b>ducts</b> (modified apocrine glands)	Presence of smooth muscle differentiates from axilla
Axilla	<b>Apocrine glands</b> (abundant)	–
Back	Thick dermis (extends deeper than other sites); broad fascicles of collagen	Most commonly asked to distinguish from scleredema, which has prominent mucin between widely spaced collagen fibers
Ear	Thin epidermis, <b>cartilage</b> , and numerous <b>vellus hairs</b> (small caliber hairs with bulbs situated in dermis)	Accessory tragus: domed papule w/ identical histologic features
Eyelid	Dermis contains only loosely arranged collagen, lacks subcutaneous fat, and <b>superficially located skeletal muscle</b>	Eyelid skin + foamy histiocytes in dermis = <b>xanthelasma</b>
Lip (dry vermillion)	Keratinizing epidermis (has stratum corneum) with granular layer; <b>skeletal muscle</b> (main clue)	–
Lip (wet mucosa)	<b>Pale keratinocytes</b> (glycogen rich), <b>nonkeratinizing</b> (lacks stratum corneum), minor salivary glands (basaloid), <b>lacks granular layer</b> , and lacks hair follicles ( <b>glabrous</b> )	Vulvar mucosa appears similar (but no salivary glands or skeletal muscle) Parakeratotic scale is seen in oral LP (clue to abnormal mucosa)
Nose	Abundant <b>sebaceous glands</b>	–
Palms/soles	Massively thickened stratum corneum, <b>compact orthohyperkeratosis</b> ; <b>Meissner's corpuscles</b> in dermal papillae; lacks hair follicles ( <b>glabrous</b> )	–
Scalp	<b>Numerous terminal hairs</b> w/ deeply situated bulbs (SQ fat)	–



**Table 7-2.** High-Yield Derrpath Bodies/Cells

Body	Description	Associated Disease(s)/ Comments
Antoni A	Cellular area of schwannomas; has abundant <b>Verocay bodies</b>	Schwannoma (neurilemmoma)
Antoni B	Hypocellular area of schwannomas; has loose myxoid stroma and low cellularity	Schwannoma (neurilemmoma)
Asteroid bodies	Star-shaped, eosinophilic intracytoplasmic inclusions	<b>Sarcoid</b> and other granulomatous disorders
Balloon cells	Clear-appearing cells with vesicular cytoplasm, and small hyperchromatic nucleus w/ pseudonuclear inclusions	Balloon cell nevus, balloon cell melanoma (has classic features of melanoma in junctional component)
Banana bodies	Crescentic golden <b>yellow-brown (ochre) fibers</b> , in dermis	Endogenous ochronosis ( <b>alkaptonuria</b> ) > exogenous ochronosis (from <b>hydroquinone</b> ) Endogenous ochronosis is as a result of deposition of <b>homogentisic acid</b> on collagen and cartilage
Bean bag cells	Histiocytes that have engulfed WBCs, RBCs, and nuclear debris ( <b>cytophagocytosis</b> )	<b>Cytophagic histiocytic panniculitis</b> , subcutaneous panniculitis-like T-cell lymphoma (SPTCL), lupus profundus, and hemophagocytic lymphohistiocytosis (HLH)
Birbeck granules	Only seen on electron microscopy; classically appear as <b>tennis racket</b> structures or rods	Pathognomonic of Langerhans cells and <b>LCH cells</b> <b>Langerin (CD207)</b> is the major component of Birbeck granules → Langerin immunostain is the <b>most specific</b> stain (> CD1a) for LCH cells and Langerhans cells
Caterpillar bodies	Eosinophilic material comprised of <b>BMZ material (PAS+ and collagen IV+)</b> , found in <b>roof of blisters</b> and basal layer of epidermis	<b>PCT, EPP</b> Caterpillar bodies are comprised of the same material as Kamino bodies (Spitz nevi)
Cholesterol clefts	Elongated, needle-shaped clear spaces once occupied by cholesterol (cholesterol, itself, is removed by paraffin embedding)	<u>Within adipocytes (radiating pattern):</u> <b>SQ fat necrosis of newborn, sclerema neonatorum, and poststeroid panniculitis</b> <u>Within dermis:</u> <b>NXG</b> (> NLD), plane xanthoma, and eruptive xanthoma <u>Within arterioles:</u> <b>cholesterol embolism</b> (fibrin thrombus surrounds cholesterol)
Cigar bodies	Oval yeast ( <b>PAS+</b> and GMS+)	Sporotrichosis May also see " <b>sporothrix asteroid</b> " bodies = yeast with radiating pink hyaline material (immune complexes on yeast surface)
Civatte/colloid/cytoid bodies	Apoptotic keratinocytes (eosinophilic)	<b>Lichen planus</b> classically, but seen in all interface dermatitides
Clover leaf (flower) cells	Atypical T-lymphocytes with a cloverleaf or flower-like nucleus; seen in peripheral blood	HTLV-induced adult T-cell lymphoma (pathognomonic)
Comma-shaped bodies	Comma-shaped electron dense membranes seen within histiocytes (electron microscopy)	Classically associated with (a/w) <b>benign cephalic histiocytosis</b> (but also seen in JXG)
Corps ronds/ grains	Two special types of dyskeratotic keratinocytes: <u>Ronds:</u> single or grouped, round keratinocytes with a <b>perinuclear halo</b> , brightly eosinophilic cytoplasm, and pyknotic nucleus; found in <b>spinous layer</b> >stratum corneum <u>Grains:</u> smaller, flattened keratinocytes resembling parakeratosis; found in <b>granular layer/stratum corneum</b>	<b>Darier's disease, warty dyskeratoma</b> , Grover's, Hailey-Hailey (less prominent), acantholytic dyskeratotic acanthoma (trunk is #1 site), papular acantholytic dyskeratosis (multiple lesions on vulva, mistaken for condyloma), and PRP (focally)
Cowdry A body	Intranuclear inclusions (eosinophilic globules) surrounded by halo	<b>HSV, VZV</b> , and CMV ("owl's eye" endothelial cells)
Cowdry B body	Intranuclear inclusions	<b>Poliovirus</b> > adenovirus
Donovan bodies	Intracytoplasmic " <b>safety pin</b> "-shaped bacteria in macrophages	Granuloma inguinale
Dutcher body	Pseudo-intranuclear pink mass of immunoglobulins within plasma cells	Classically a/w <b>malignant B-cell processes: B-cell lymphoma, multiple myeloma</b> , and Waldenstrom's macroglobulinemia Mnemonic: <b>Dutcher</b> = <b>D</b> ead (a/w malignant process), vs Russell bodies (a/w benign conditions; "happy, pregnant plasma cells")
Flame figures	<b>Major basic protein</b> from eosinophils deposited on collagen	<b>Wells syndrome</b> , dermal hypersensitivity reaction (exaggerated arthropod assault, drug), and bullous pemphigoid (rarely) Neutrophilic processes (esp. PNGD, RA) can have <b>bluish-purple "flame figure-like"</b> structures as a result of <b>neutrophilic debris</b> deposited on collagen
Floret cells	Multinucleated giant cells with peripherally located overlapping nuclei ( <b>resembles flower</b> ) and "smudgy"/indistinct chromatin	<b>Pleomorphic lipoma</b>

**Table 7-2.** High-Yield Dermopath Bodies/Cells—cont'd

Body	Description	Associated Disease(s)/ Comments
Gamma-Favre body	Intracytoplasmic basophilic inclusions within endothelial cells	Lymphogranuloma venereum
Gaucher cells	Glucocerebroside-laden histiocytes ("crinkled tissue paper-like histiocytes")	Gaucher's disease
Ghost/ shadow cells (pilomatricoma)	<b>Anucleate</b> , eosinophilic, keratinized cells with a ghost-like outline where the nucleus previously resided; often surrounded by transitional cells and basaloid cells	Pilomatricoma
Ghost cells (pancreatic panniculitis)	Blue-purple calcium outlines remnants of necrotic lipocytes	<b>Pancreatic panniculitis</b>
Globi	Amphophilic, encapsulated collections of mycobacteria	<b>Lepromatous leprosy</b> Other leprosy buzzword: <b>Virchow cells</b> (pale, foamy histiocytes parasitized by <i>M. leprae</i> )
Glomus bodies	Specialized A-V shunts that bypass capillaries; mostly found on <b>fingers and toes</b> ; responsible for <b>temperature regulation</b>	Glomus tumor: solid nodular proliferation of glomus cells; favors fingers and toes Glomangiomas: ectatic vascular malformation w/ fewer glomus cells than glomus tumor; widespread anatomic distribution
Guarnieri body	Eosinophilic cytoplasmic inclusions	Smallpox
Hallmark (horseshoe) cells	Markedly atypical; large T-lymphocytes with a horseshoe-shaped nucleus	Anaplastic Large Cell Lymphoma ( <b>ALCL</b> ) and LyP (type C)
Henderson-Paterson bodies	Pink intracytoplasmic inclusions	<b>Molluscum contagiosum</b>
Kamino bodies	Collections of amorphous eosinophilic/hyaline <b>BMZ material (PAS+ and collagen IV+)</b> in tips of dermal papillae and within epidermis	Spitz nevi Large aggregates of Kamino bodies are rarely, or perhaps never, seen in melanoma!
Koilocytes	Keratinocytes w/ viral cytopathic changes ( <b>perinuclear halo, shrunken hyperchromatic nucleus</b> , and irregular nuclear contours)	<b>HPV</b> Unlike pap smears, true koilocytes are not always seen in HPV skin infections → may just see <b>vacuolated keratinocytes</b> and coarse keratohyaline granules
Langhans giant cells	Histiocytic giant cells with a peripheral ("horse-shoe") arrangement of nuclei	Classically a/w <b>tuberculosis</b> , but often seen in sarcoidosis and other granulomatous diseases Not to be confused with LangERhans cells!
Mariner's wheel	Central round yeast (60 µm) w/ multiple radiating buds	<b>Paracoccidioidomycosis</b> ("South American Blastomycosis", <i>Paracoccidioides brasiliensis</i> )
Max-Joseph (Caspary-Joseph) spaces	<b>Focal clefts at DEJ</b> formed by extreme damage to basal layer from interface dermatitis	<b>Lichen planus</b> Exaggerated Max-Joseph spaces → bullous LP
Medlar bodies	Thick-walled clusters of <b>brown round yeast</b> forms (" <b>copper pennies</b> ")	<b>Chromomycosis</b> Differential Diagnosis (DDx): <b>pigmented hyphae</b> are seen in phaeohyphomycosis
Michaelis-Gutmann body	<b>Round, calcified</b> , and laminated bacterial remnants	<b>Malakoplakia</b>
Miescher's radial granuloma	Small granuloma comprised of <b>radially arrayed histiocytes around a central cleft</b> ; located in <b>fat septae</b>	<b>Erythema nodosum</b> Do not confuse with "Miescher's granuloma" (aka actinic granuloma of O'Brien, or annular elastolytic giant cell granuloma)
Mikulicz cells	Foamy histiocytes containing gram(-) rods ( <b><i>Klebsiella rhinoscleromatis</i></b> )	<b>Rhinoscleroma</b> Other rhinoscleroma buzzword: Russell bodies
Mulberry cells	Large <b>pink/red-colored</b> fat cells with a <b>central nucleus</b> (vs peripheral in normal adipocytes) and a multivacuolated, <b>granular, eosinophilic</b> cytoplasm	<b>Hibernoma</b> Tumor of <b>brown fat</b> ; most common in adults on neck and upper back
Morula	Organism (2–11 µm) with numerous internal septations → appears similar to morula stage of embryogenesis or like a " <b>soccer ball</b> "; <b>PAS+</b> and <b>GMS+</b>	<b>Protothecosis</b> (an achloric alga)
Negri body	Neuronal inclusion	Rabies
Odland (lamellar) bodies	<b>Oval granules w/ lamellar organization</b> seen w/ <b>electron microscopy</b> ; contain phospholipids, glycoproteins and acid phosphatases; found in upper spinous and granular layer; major role in <b>barrier function</b> and keratinocyte cohesion	<b>Harlequin fetus</b> (absent), <b>Flegel's disease</b> (decreased or absent)

Continued

**Table 7-2.** High-Yield Derrpath Bodies/Cells—cont'd

Body	Description	Associated Disease(s)/ Comments
Papillary mesenchymal bodies	<b>Condensed clusters of fibroblasts</b> adjacent to basaloid epithelial follicular buds; recapitulates appearance of normal hair bulb (dermal papilla-hair matrix)	<b>Trichoepithelioma, desmoplastic trichoepithelioma</b> , and trichoblastoma Absent in BCC
Psammoma body	Concentric, calcified laminated spheres	<b>Meningioma</b> , mesothelioma, ovarian cancer, <b>papillary thyroid cancer</b> , and ovarian cancer
Pustulo-ovoid bodies of Milian	<b>Round eosinophilic cytoplasmic inclusions</b> comprised of <b>lysosomes</b> /Golgi material ( <b>PAS+</b> and <b>diastase-resistant</b> )	<b>Granular cell tumor</b>
Reed-Sternberg cells	Large atypical lymphoid cells derived from germinal center <b>B-cells</b> ; characteristic <b>bilobed nucleus w/ prominent central nucleolus</b> within each nucleus → <b>“owl's eye”</b> appearance; <b>CD30+</b> , <b>CD15+</b> , and <b>PAX-5+</b> (B-cell origin)	Hodgkin's lymphoma
Reed-Sternberg-like cells	Appear similar to Reed-Sternberg cells on H&E, but are <b>T-cells</b> ; <b>CD3+</b> , <b>CD4+</b> , <b>CD30+</b> , and <b>CD15-</b>	<b>Lymphomatoid papulosis</b> , ALCL
Rocha-Lima bodies	Intracytoplasmic inclusions within endothelial cells	Oroya fever, verruga peruana
Russell bodies	Intracytoplasmic immunoglobulin collections (eosinophilic) stuffing the cytoplasm of plasma cells	<b>Rhinoscleroma, Granuloma inguinale</b> Russell bodies are classically a/w benign diagnoses (“happy, pregnant plasma cells”) vs malignant associations for Dutcher bodies
Schaumann bodies	Calcified laminated collections	Sarcoid
Sezary cells	Atypical lymphocytes with <b>cerebriform</b> nuclei	<b>Sezary syndrome</b> , MF
Signet ring cells	Cell with eccentric nucleus and large pool of intracytoplasmic mucin (pushes nucleus to periphery)	Any mucin-producing adenocarcinoma (usually metastatic if seen in skin)
Sunburn cells	<b>Dyskeratotic keratinocytes</b> scattered in upper and mid-epidermis (> basal layer)	Sunburns and <b>phototoxic drug</b> eruptions
Touton giant cells	Large, multinucleated histiocytes with <b>wreath-like</b> arrangement of nuclei and peripheral cytoplasmic lipid	<b>JXG</b> (and other xanthomas), <b>dermatofibroma</b> (often contain hemosiderin) Boards pearl: Touton giant cells are ubiquitous in DF, but not seen in DFSP!
Verocay bodies	Two stacked rows of elongated <b>palisading nuclei surrounding amorphous pink material</b> (cytoplasmic processes of Schwann cells); seen in hypercellular (Antoni A) areas of schwannomas	Schwannoma (neurilemmoma)
Virchow cells	Foamy histiocytes parasitized by acid fast bacilli	<b>Lepromatous leprosy</b> Other boards buzzword: globi (encapsulated amphophilic masses of <i>M. leprae</i> )
Von Hanseman cells	Large histiocytes with granular eosinophilic cytoplasm; the cytoplasm of these cells contains Michaelis-Gutmann bodies	<b>Malakoplakia</b>
Weibel-Palade bodies	Cytoplasmic organelle of endothelial cells seen only with EM; contains <b>vWF</b> and P-selectin	von Willebrand' disease is caused by qualitative or quantitative vWF deficiency

**Table 7-3.** Most Commonly Used Special Stains

Stain	Target	Color(s)	Comments
<b>Collagen/elastic fibers</b>			
Verhoeff-van Gieson (VVG)	Elastic fibers Collagen Rest of connective tissue	Black Red Yellow	Most commonly used collagen/elastin stain Distinguishes between various perforating diseases
<b>Smooth muscle</b>			
Masson trichrome	Collagen fibers Smooth muscle	Blue or green Red	Stains the inclusions ( <b>red</b> ) in <b>infantile digital fibromatosis</b>
Movat's pentachrome	Elastic fibers Collagen Smooth muscle, fibrin	Black Yellow Red	Stains the inclusions (red) in infantile digital fibromatosis

**Table 7-3.** Most Commonly Used Special Stains—cont'd

Stain	Target	Color(s)	Comments
Phosphotungstic acid hematoxylin (PTAH)	Collagen Smooth muscle, fibrin	Red Blue	Stains the inclusions (blue) in infantile digital fibromatosis
<b>Lipids (all stains must be performed on frozen tissue only! → not commonly used)</b>			
Oil-red-O	Lipids	Red	–
Sudan black B	Lipids	Black	–
Scarlet red	Lipids	Red-brown	–
<b>Iron/Hemosiderin</b>			
Perls/Prussian blue	Hemosiderin/iron	Blue	Most commonly used in conjunction with Fontana-Masson stain to distinguish between melanin (black w/ Fontana-Masson) and hemosiderin pigment Does not stain iron in intact RBCs → does not work well for talon noir
<b>Calcium</b>			
Von Kossa	Calcium (salts)	Brown-black	Most commonly used “calcium stain,” but actually stains the anions rather than calcium itself → less calcium-specific than Alizarin red
Alizarin red	Calcium	Red-orange	More specific for calcium than Von Kossa
<b>Mucin</b>			
Alcian blue pH 0.5	Sulfated acid MPS (heparin, chondroitin, and dermatan sulfates)	Blue	In normal skin, most mucin is sulfated acid MPS Hyaluronic acid (nonsulfated acid MPS) does not stain with Alcian blue at pH 0.5
Alcian blue pH 2.5	Nonsulfated acid MPS (hyaluronic acid)	Blue	In diseases w/ ↑mucin (lupus, GA, and follicular mucinosis), most mucin is hyaluronic acid Mnemonic: <b>“HIGH-luronic acid stains with Alcian Blue at HIGH pH (pH 2.5) only!”</b> Sulfated acid MPS stain with Alcian blue at both pH 2.5 and pH 0.5
Colloidal iron	Acid MPS (sulfated and nonsulfated)	Blue	Hyaluronidase may be added to distinguish between hyaluronic acid and other mucin types
Mucicarmine	Epithelial mucin	Pink-red	Used primarily for sialomucin, adenocarcinoma, Paget’s disease, and Cryptococcus (capsule) Not a good stain for dermal mucins
Periodic acid Schiff (PAS)	Neutral MPS (basement membrane), fungi, and glycogen	Pink	Primarily used to highlight BMZ material Does not stain acid MPS (hyaluronic acid and other mucins)
Toluidine blue	Acid MPS	Red-purple (“metachromatic staining”: stains tissue a different color than blue color of stain)	Rarely used as a mucin stain → more commonly used as mast cell stain
<b>Amyloid</b>			
Congo red	Amyloid	Pink-red; <b>apple green birefringence</b> when polarized	Most commonly used amyloid stain In real world, not always reliable for macular/lichen amyloid
Thioflavin T	Amyloid (fluorescence microscopy)	Yellow-green	Requires fluorescence microscopy
Cresyl violet	Amyloid	Red	Of note, cotton dyes (e.g., Pagoda red or Dylon) also stain amyloid
<b>Melanin</b>			
Fontana-Masson (silver stain)	Melanin	Black	Most commonly used in conjunction w/ Perls stain to distinguish hemosiderin vs melanin Vitiligo has complete loss of epidermal staining
Silver nitrate	Melanin	Black	–

Continued



**Table 7-3.** Most Commonly Used Special Stains—cont'd

Stain	Target	Color(s)	Comments
<b>Mast cell stains (all except Leder stain and c-KIT are unreliable in degranulated skin → use Lidocaine without epinephrine to avoid mast cell degranulation)</b>			
Leder (chloracetate esterase)	Mast cell cytoplasm and granules	Red	Unlike other mast cell stains, it is <b>NOT dependent on presence of mast cell granules</b> → effective even in degranulated skin Only Leder and c-KIT (CD117) are reliable in degranulated skin
Tryptase (immunostain, but is discussed here for convenience)	Mast cell granules	Brown or red (color depends on type of peroxidase used)	Dependent on presence of mast cell granules
Giemsa	Mast cell granules	Purple-blue (metachromatic)	Dependent on presence of mast cell granules
Toluidine blue	Mast cell granules	Purple (metachromatic)	Dependent on presence of mast cell granules
<b>Microbial Stains</b>			
Periodic acid Schiff (PAS)	Fungi, neutral MPS (basement membrane), and <b>glycogen</b>	Pink	Positive in <b>clear cell acanthoma</b> and <b>trichilemmoma</b> , as a result of ↑glycogen → becomes negative if add diastase (PAS-D) Does not stain acid MPS (hyaluronic acid and other mucins)
Periodic acid Schiff w/ diastase (PAS-D)	Fungi, neutral MPS (basement membrane)	Pink	Helpful for demonstrating BMZ thickening (lupus, DM), and thickened vessel walls of porphyria
Gomori methenamine silver (GMS; a silver stain)	Fungi	Black (stains fungal wall)	Green background (counterstain)
Gram stain (Brown-Hopps and Brown-Brenn)	Gram(+) bacteria Gram(−) bacteria	Blue Red	Gram(−) bacteria not well-visualized in skin biopsies
Fite	<i>M. leprae</i> , <i>Nocardia</i> , and atypical mycobacteria	Red	Stain of choice for "partially acid-fast" organisms ( <b><i>M. leprae</i></b> , <i>Nocardia</i> ), and <b>atypical mycobacteria</b> because these are over-decolorized by Ziehl-Neelsen Peanut oil and gentle decolorization process allows for better color preservation than in Ziehl-Neelsen
Ziehl-Neelsen	Acid-fast bacteria	Red	Most commonly used AFB stain <b>Less effective for <i>M. leprae</i> and atypical AFB</b> → use Fite instead
Auramine-rhodamine	Acid-fast bacteria	Yellow fluorescence	Requires fluorescence microscopy
Warthin-Starry (silver stain)	Spirochetes (syphilis, <i>Borrelia</i> )	Black	Also stains organisms in bacillary angiomatosis, granuloma inguinale (Donovan bodies), and rhinoscleroma Disadvantage: nonspecific ("dirty") staining pattern → has been largely replaced by spirochete immunostain
Steiner (silver stain)	Spirochetes (syphilis, <i>Borrelia</i> )	Black	Same staining pattern as Warthin-Starry
Giemsa	<b>Leishmania</b> , Histoplasma, and Rickettsia	Purple-blue	–
<b>Other Stains</b>			
Bodian	Nerve axons (filaments)	Black	Positive in neurofibromas, traumatic neuromas, and PEN; <b>negative in schwannoma</b> (lacks axons)
Methyl green pyronin	RNA DNA	Pink Blue-green	Requires frozen tissue
Feulgen	DNA	Red-purple	–

**Table 7-4.** Characteristic Immunostains by Cell Type

Cell Type	Immunostain
B-lymphocytes	<b>CD20</b> (most commonly used B-cell marker; absent in plasma cells; target for rituximab), <b>PAX-5</b> (more sensitive and specific than CD20), <b>CD79a</b> (B-cells and plasma cells), <b>CD19</b> (useful in monitoring response to rituximab therapy, because CD20-negative B-cells may arise following therapy), CD45 (LCA; expressed on all hematopoietic cells except platelets and RBCs), and IgG light chains ( $\kappa$ and $\lambda$ )
Dermal dendritic cells	Two distinct populations: <u>Type I: factor XIIIa<sup>+</sup></u> ; reside in papillary dermis; involved in phagocytosis, antigen presentation, and wound healing; abundant in <b>dermatofibroma</b> <u>Type II: CD34<sup>+</sup></u> ; reside in reticular dermis; <b>CD34 expression is lost in scleroderma/morphea</b> , and $\uparrow$ in NSF; scleromyxedema * Notable CD34 <sup>+</sup> tumors in dermpath: <b>DFSP</b> , <b>spindle cell lipoma</b> /pleomorphic lipoma, <b>Kaposi sarcoma</b> (endothelial cells), <b>neurofibroma</b> (diffuse NF can be misdiagnosed as DFSP!), <b>fibrofolliculoma/trichodiscoma</b> , <b>trichilemmoma/DTL</b> (epithelial cells), <b>solitary fibrous tumor</b> , <b>leukemia cutis</b> (less sensitive than CD43, c-KIT, CD68, lysozyme, MPO), Kaposiform hemangioendothelioma (endothelial cells), epithelioid hemangioendothelioma (endothelial cells), sclerotic fibroma, pleomorphic fibroma, superficial angiomyxoma, superficial acral fibromyxoma (and cellular digital fibroma), cellular angiofibroma of vulva/genital region, and ischemic fasciitis
Endothelial cells	<b>CD31</b> (previous gold standard for endothelial cells $\rightarrow$ recently superseded by ERG and FLI-1), <b>CD34</b> (less specific than CD31), <b>ERG</b> (excellent new stain; very sensitive and specific), <b>FLI-1</b> (nuclear stain; improvement over CD31 and CD34 but not as good as ERG), <i>Ulex europaeus</i> agglutinin 1, factor VIII ag, and vimentin
Fibroblasts	Vimentin, procollagen I (also expressed in DFSP, AFX, NSF, and scleromyxedema)
Histiocytes/ macrophages	<b>CD68</b> , <b>CD163</b> (more specific than CD68), <b>lysozyme</b> , $\alpha$ -1 antitrypsin, HAM-56 <sup>+</sup> (especially JXG and related xanthogranulomas), CD11b, CD14b, factor XIIIa, MAC-387 (true macrophages), and vimentin
Keratinocytes	<b>Cytokeratin</b> and p63
Langerhans cells	<b>S100</b> , <b>CD1a</b> , <b>Langerin</b> ( <b>CD207</b> ; stains Birbeck granules $\rightarrow$ extremely specific), peanut agglutinin, and vimentin
Lymphatics	<b>D2-40</b> (podoplanin), <b>LYVE-1</b> (negative in blood vessel endothelium), and vimentin
Mast cells	<b>c-KIT</b> ( <b>CD117</b> ) and <b>tryptase</b>
Melanocytes	<b>S100</b> , <b>HMB-45</b> (gp100; less sensitive but more specific than S100; typically negative in desmoplastic melanoma), <b>MART-1/Melan-A</b> (less sensitive but more specific than S100; typically negative in desmoplastic melanoma), <b>MITF</b> (nuclear stain; positive in only 30% of desmoplastic melanomas), <b>p16</b> (positive in Spitz nevi; often lost or diminished in spitzoid melanoma and ASTs), <b>p75/NGFR</b> (useful in desmoplastic melanoma, especially when S100 is negative), <b>Sox10</b> (nuclear stain; helpful in distinguishing desmoplastic melanoma from scar tissue), tyrosinase, and vimentin
Merkel cells	<b>CK20</b> (perinuclear-dot pattern), neurofilament (extremely useful and under-utilized stain; especially helpful for CK20-negative Merkel cell carcinomas), and NSE
Myofibroblasts	<b>SMA</b> (“tram-track” pattern); myofibroblasts do not express desmin (vs true smooth muscle cells)
Natural killer cells	<b>CD56</b> (most commonly used), CD57, <b>granzyme A/B</b> , and <b>TIA-1</b> (latter 2 stains are also positive in cytotoxic T-cells)
Nerves	<u>Axons: neurofilament</u> and NSE <u>Schwann cells: S100</u> , GFAP, and MBP
Neutrophils	<b>MPO</b> (myeloperoxidase; especially useful stain in histiocytoid Sweet’s)
Plasma cells	<b>CD138</b> , CD79a, and CD45
Plasmacytoid dendritic cells	<b>CD123</b> Plasmacytoid dendritic cells are $\uparrow$ in <b>lupus</b> (but not in dermatomyositis) and $\uparrow$ in <b>GA</b> ( $\gg$ NLD, rheumatoid nodules)
Sebaceous glands	<b>EMA</b> , <b>adipophilin</b> , <b>androgen receptor</b> , and cytokeratin
Smooth muscle	<b>SMA</b> (diffuse pattern), <b>desmin</b>
Sweat glands	CEA, EMA, GCDFP-15 (apocrine $>$ eccrine), and cytokeratin
T-lymphocytes	CD2, <b>CD3</b> (most specific cell marker), CD4, CD5, CD7, CD8, CD45 (LCA), <b>CD45Ra</b> (naïve T-cells), <b>CD45Ro</b> (memory T-cells; positive in MF), and FOXP3 (T regulatory cells)

**Table 7-5.** Most Commonly Used Epithelial Immunostains

Immunostain	Description/Staining Pattern	Comments
AE1/AE3	Cocktail of low (AE1) and high (AE3) molecular weight keratin antibodies; typically positive in all epithelial tumors	Helps confirm diagnosis of SCC and adnexal carcinomas <b>Often fails to stain sarcomatoid SCC</b> $\rightarrow$ need additional cytokeratin stains (MNf116, CK903, or CK5/6), p63 or p40 to diagnose high-grade/sarcomatoid SCC
MNF116	Newer pankeratin immunostain w/ better sensitivity than AE1/AE3; stains all epithelial tissue	Helps differentiate <b>high-grade/sarcomatoid SCC</b> (positive) vs AFX (negative)
CK5/6	High MW keratin immunostain; stains lower level of epidermis	Positive in primary cutaneous SCCs and adnexal carcinomas, but negative in metastatic lesions $\rightarrow$ distinguishes <b>primary cutaneous adnexal CA</b> (positive) vs. metastatic adenocarcinomas from internal organs (negative) Helps differentiate <b>high-grade/sarcomatoid SCC</b> (positive) vs. AFX (negative)

Continued

Table 7-5. Most Commonly Used Epithelial Immunostains—cont'd		
Immunostain	Description/Staining Pattern	Comments
CAM5.2	Low MW keratin immunostain directed against <b>CK8/18</b> ; stains <b>glandular epithelium</b> ; negative in squamous epithelium (including epidermis)	Positive in <b>Paget's and EMPD</b> , and eccrine glands/neoplasms
CK7	Stains glandular epithelium	Positive in <b>Paget's and EMPD</b> Also used in conjunction with CK20 to determine <b>origin of metastatic adenocarcinoma</b> : CK7+ = malignancy <b>above the diaphragm</b> (breast, lung) CK20+ = malignancy <b>below diaphragm</b> (stomach, colon)
EMA (epithelial membrane antigen)	Stains normal skin adnexae	Positive in <b>Paget's and EMPD</b> , adnexal neoplasms (including <b>sebaceous carcinoma</b> ), most SCCs, and <b>epithelioid sarcoma</b> (INI-1 loss and EMA positivity are the two classic stains!)
CEA	Stains normal sweat glands (eccrine and apocrine); positive in sweat gland neoplasms	Positive in <b>Paget's and EMPD</b>
Ber-EP4	Stains nonkeratinizing epithelial cells	Differentiates between <b>BCC</b> (positive), SCC (always negative), and sebaceous carcinoma (usually negative)
p63	Homologue of p53 that is positive in normal epidermis and adnexal epithelium	Stains >90% of adnexal neoplasms (benign and malignant) Differentiates between <b>primary cutaneous adnexal carcinomas</b> (positive) and metastatic adenocarcinomas involving the skin (negative) Also stains <b>high-grade/sarcomatoid SCC</b> (distinguishes from AFX)

Table 7-6. Artifacts and Effects of Exogenous Materials	
Inciting Cause	Histologic Features
Cryotherapy/freezing artifact	Keratinocyte vacuolization, subepidermal blister, homogenization of epidermis
Electrocautery artifact	Vertically oriented parallel keratinocytes (Fig. 7-1)
Gelfoam	Purple, angulated foreign material with surrounding granulomatous inflammation foreign material with surrounding granulomatous reaction (Fig. 7-2)
Suture granuloma	Foreign body granuloma surrounding suture material (polarized light may show birefringence)
Intralesional corticosteroids	Amorphous, homogenous white material +/- surrounding fibrous capsule
Fillers	Features depend on specific filler (see Fig. 7-3 to 7-7 and corresponding captions for details) (Figs. 7-3–7-7)

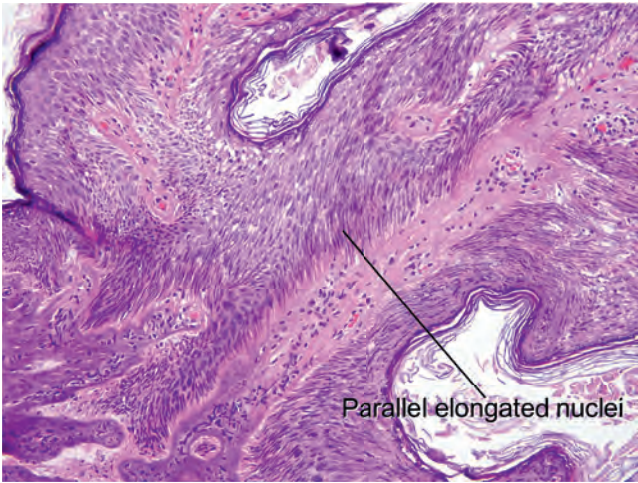


Figure 7-1. Electrocautery. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

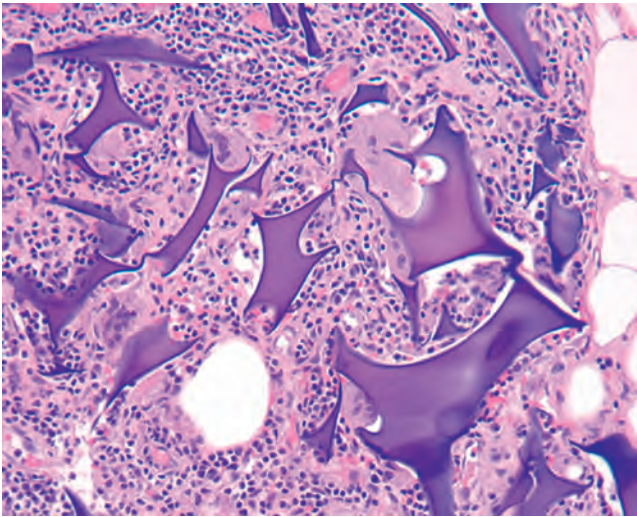


Figure 7-2. Gelfoam, purple, angled deposits. (From Weedon D. *Weedon's Skin Pathology*, 3rd ed. Elsevier. 2009)

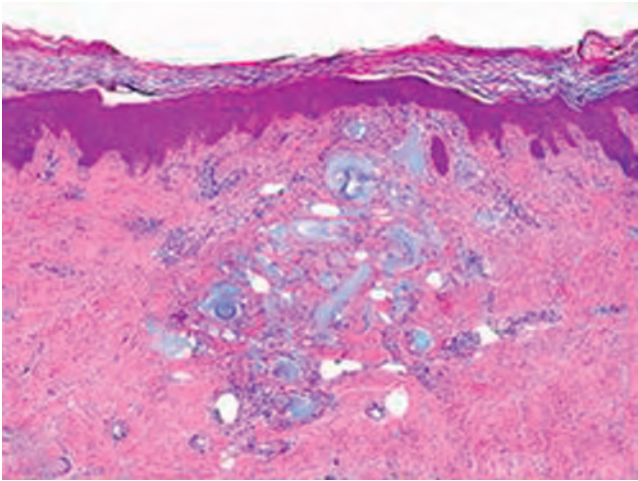
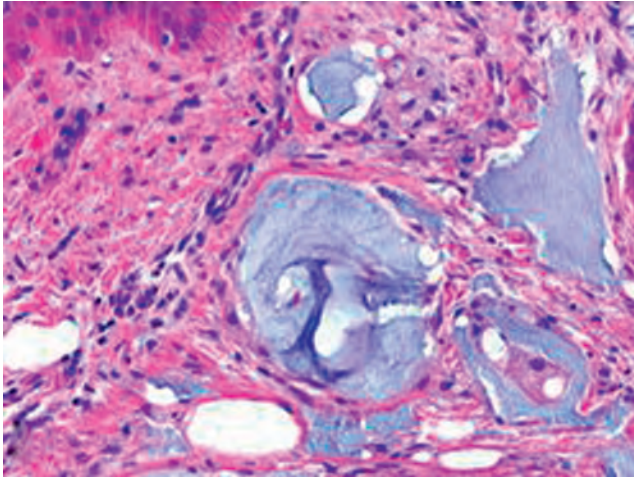
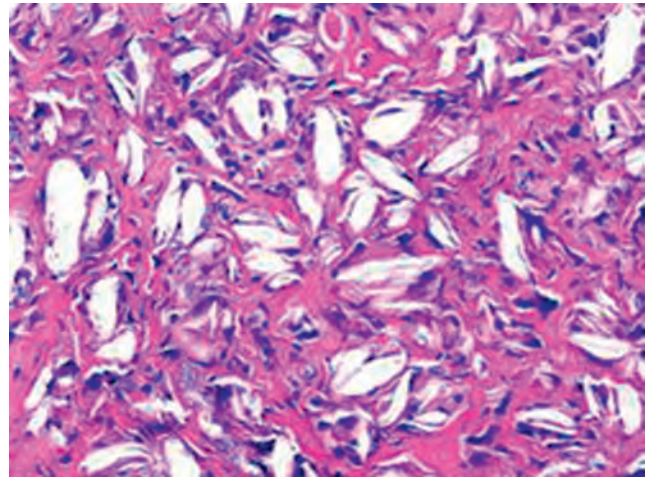


Figure 7-3. Histopathologic features of a granulomatous reaction to hyaluronic acid. Low power view showing basophilic material at different levels of the dermis. (From Requena et al. *Adverse reactions to injectable soft tissue fillers*. J Amer Acad Dermatol 2010;64:6:1178)

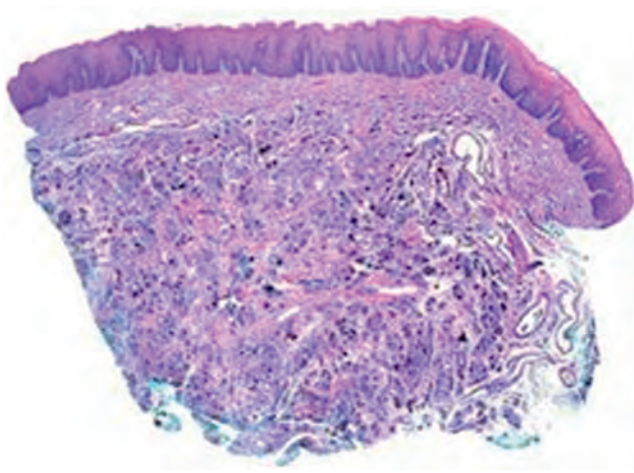




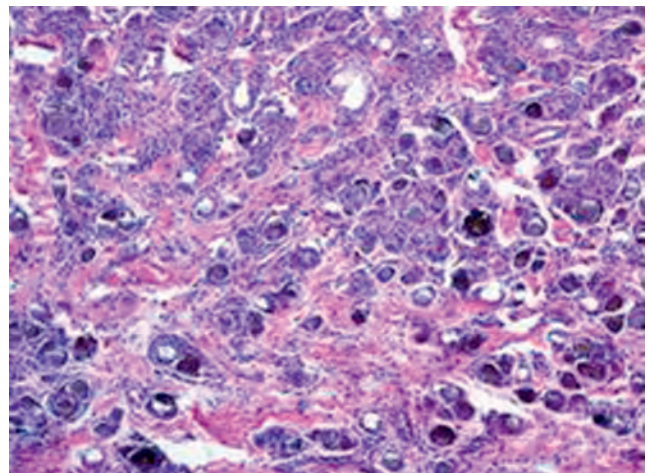
**Figure 7-4.** Histopathologic features of a granulomatous reaction to hyaluronic acid. Basophilic material is surrounded by histiocytes and multinucleated giant cells. (From Requena et al. Adverse reactions to injectable soft tissue fillers. *J Amer Acad Dermatol* 2011;64:6:1178)



**Figure 7-5.** Histopathologic features of granulomatous reaction to New-Fill (Dermik Laboratories, Berwyn, PA). Most of the particles show fusiform or oval shape. (From Requena et al. Adverse reactions to injectable soft tissue fillers. *J Amer Acad Dermatol* 2011;64:6:1178)



**Figure 7-6.** Histopathologic features of granuloma secondary to injections of calcium hydroxylapatite microspheres. Scanning power showing a diffuse involvement of the corium of the oral mucosa. (From Requena et al. Adverse reactions to injectable soft tissue fillers. *J Amer Acad Dermatol* 2010;64:6:1178)



**Figure 7-7.** Histopathologic features of granuloma secondary to injections of calcium hydroxylapatite microspheres. Granulomas surrounding the calcium hydroxylapatite microspheres. (From Requena et al. Adverse reactions to injectable soft tissue fillers. *J Amer Acad Dermatol* 2011;64:6:1178)

**Table 7-7.** Spindle Cell Neoplasms

	CK	Vimentin	S100	SMA
SCC	+	–	–	–
Leiomyosarcoma	–	+	–	+
				(also desmin+)
AFX	–	+	–	–
Melanoma	–	+	+	–

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

**Table 7-8.** Neoplasms with Pagetoid Scatter

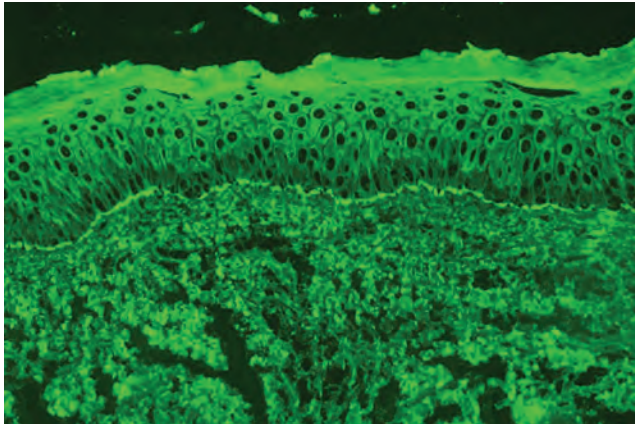
	CK	CEA	S100	LCA
Bowen's	+	–	–	–
Paget's/EMPD	+	+	–	–
MF	–	–	–	+
Melanoma	–	–	+	–
Sebaceous carcinoma	+	+	–	–

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



**Table 7-9.** Epithelial Carcinomas

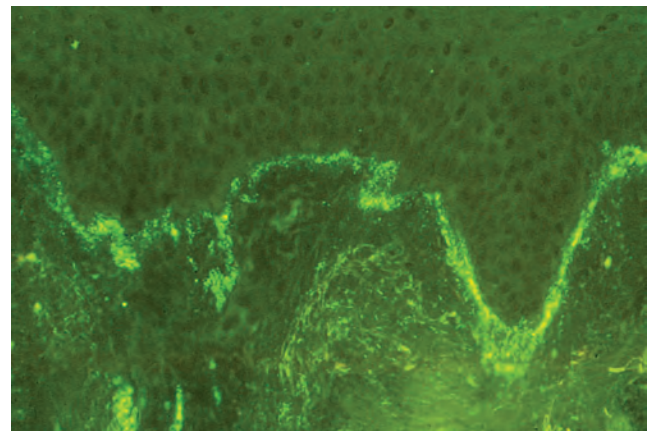
	Ber-EP4	EMA	Androgen Receptor	Adipophilin
SCC	–	+	–	–
BCC	+	–	–	–
Sebaceous CA	–	+	+	+



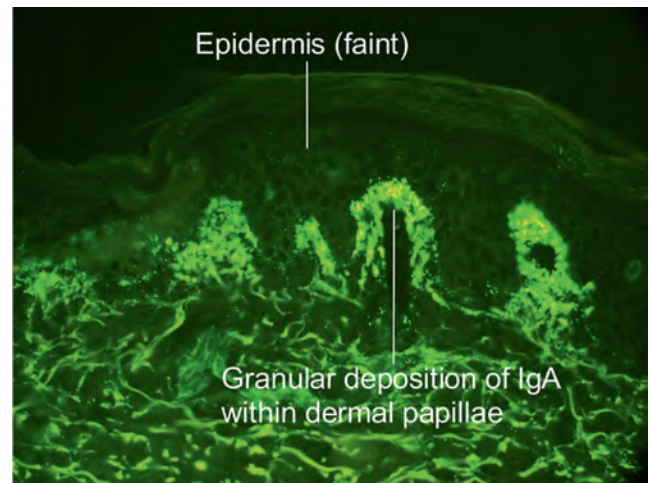
**Figure 7-8.** Bullous pemphigoid. Direct immunofluorescence showing linear IgG along the dermal-epidermal junction. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011.)

### Immunofluorescence and related studies (Summarized in Table 7-10, Staining Characteristics of Subepidermal Blistering Diseases)

- Collagen IV immunostaining (stains the BMZ)
  - Performed on paraffin embedded sections to determine level of epidermal separation by comparing to stained BMZ
  - Is an alternative to salt-split skin immunofluorescence
  - Staining along floor of a blister: BP
  - Staining along roof of a blister: diseases targeting collagen VII (EBA and bullous SLE)
  - BE CAREFUL! Collagen IV immunostaining patterns are **OPPOSITE** of salt-split skin DIF (and IIF) patterns!
- DIF
  - Performed on fresh frozen sections obtained from a biopsy of the patient's affected/perilesional skin
  - DIF patterns:
    - Linear (Fig. 7-8)
      - ◆ C3: pemphigoid gestationis
      - ◆ IgG and C3: bullous pemphigoid, lichen planus pemphigoides, EBA, cicatricial pemphigoid, anti-p200, anti-p105, and bullous SLE  
→ NEED further studies to distinguish!!!
      - ◆ IgA: LABD
    - Granular
      - ◆ IgG, IgM, IgA, and/or C3 along BMZ = lupus band (Fig. 7-9)
      - ◆ IgA in dermal papillae: DH (Fig. 7-10)



**Figure 7-9.** Direct immunofluorescence. Granular IgM deposition along the basement membrane zone. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011)



**Figure 7-10.** Direct immunofluorescence of dermatitis herpetiformis showing granular deposition of IgA in the dermal papillae. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier, 2013)

- Intercellular
  - ◆ IgG and C3 ("pemphigus pattern"): *P. vulgaris*, *P. foliaceus*, and paraneoplastic pemphigus  
→ Need further studies and clinical to differentiate
  - ◆ IgA: IgA pemphigus
- Linear to granular BMZ and intercellular: pemphigus erythematosus (Senear-Usher)
- Linear BMZ and intercellular: paraneoplastic pemphigus
- Vessel wall staining
  - ◆ Stippled, not thickened: LCV including IgA vasculitis and HSP
  - ◆ Thickened and smooth: **porphyrias** with cutaneous involvement and pseudoporphyria; may also see linear BMZ staining in these entities!
- Salt-split skin studies (DIF/IIF): leads to a separation of the skin at the DEJ, and allows you to see where the immunoreactants are depositing; allows for

distinction between various subepidermal blistering diseases (Table 7-10, Fig. 7-12)

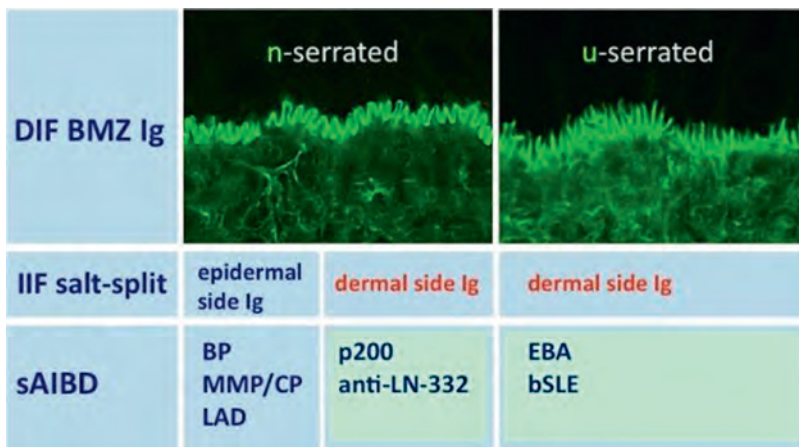
- **n-serrated/u-serrated** pattern evaluated on DIF and may be used as a substitute for salt-split skin analysis (Fig. 7-11)

- Indirect immunofluorescence (IIF): **serologic study** where blood is obtained from the patient and then tested for antibodies against skin antigens, using a normal/control sample of skin; staining patterns same as for DIF; generally less sensitive than DIF (Table 7-10)

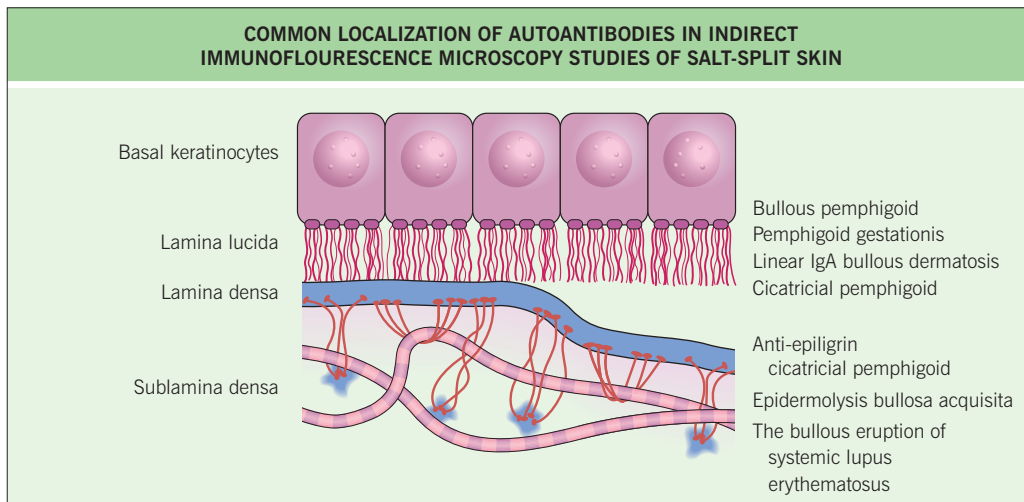
**Table 7-10.** Staining Characteristics of Subepidermal Blistering Diseases

Parameter	BP	EBA	BSLE	LAD	DH
DIF	Linear IgG, C3	Linear IgG > C3	Linear IgG, C3	Linear IgA	Granular IgA
IIF	IgG antibodies 75%–80%	IgG antibodies 25%–50%	IgG antibodies 60%	IgA antibodies 30%	Antitransglutaminase antibodies
Split skin IMF	Roof	Floor	Floor	Roof, or floor, or both	N/A
Type IV collagen	Floor	Roof	Roof	Roof or floor	N/A
EM: site of split	LL	Sub-LD	Sub-LD	LL, sub-LD, or both	Papillary dermis
Western blot	BP180 kD BP230 kD	290 kD (type VII collagen)	290 kD (type VII collagen)	BP180 kD BP230 kD 200/280 kD 285 kD 250 kD 290 kD	Antigen uncertain

*BP, bullous pemphigoid; BSLE, bullous systemic lupus erythematosus; DH, dermatitis herpetiformis; DIF, direct immunofluorescence; EBA, epidermolysis bullosa acquisita; EM, electron microscopy; IIF, indirect immunofluorescence; IMF, immunofluorescence; LAD, linear IgA disease; LL, lamina lucida; sub-LD, sub-lamina densa (From Calonje E, et al. McKee's Pathology of the Skin, 4th Ed. Elsevier. 2011)*



**Figure 7-11.** Overview a- and u-serrated pattern and different forms of subepidermal autoimmune blistering diseases (sAIBD). (From Vodegel RM, Jonkman MF, Pas HH, De Jong MCJM. Brit J of Dermatol 2004;151:1:112–118)



**Figure 7-12.** Common localization of autoantibodies in indirect immunofluorescence microscopy studies of salt-split skin. Subregions of 1 M NaCl salt-split skin commonly bound by circulating autoantibodies in patients with subepidermal immunobullous diseases. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 2nd ed. Elsevier. 2008)

## 7.2 HIGH-YIELD DERMATOPATHOLOGY DIAGNOSES AT A GLANCE (Table 7-11)

- Herein we present an abbreviated summary of the 230 most testable dermpath diagnoses, including their most

essential histopathologic features and the most likely distractor answers one may encounter on an examination

- Because of space constraints, we are unable to include histologic images of all entities; we encourage the reader to refer to one of the many excellent Elsevier Dermatopathology titles (Table 7-11).

*Text continued on p. 390*

**Table 7-11.** High-Yield Dermatopathology Diagnoses at a Glance

Dx	Buzzwords/Essential Features	Most Tested DDx
Acanthosis Nigricans	Epidermal papillomatosis	Histologically <b>identical</b> to CARP, acrokeratosis verruciformis of Hopf, and SK
Accessory digit	Pedunculated papule, <b>numerous nerve bundles</b>	Acquired digital fibrokeratoma (lacks nerves, more fibrotic), and accessory tragus (vellus hairs, cartilage, and lacks nerve bundles)
Accessory nipple	Domed papule, papillomatous surface +/- central invagination, <b>↑smooth muscle</b> , sebaceous glands opening directly onto skin surface, and <b>mammary ducts/glands</b>	Becker's nevus (lacks mammary glands and sebaceous glands opening directly onto skin surface), and normal nipple (need clinical Hx)
Accessory tragus	Polypoid, multiple <b>vellus hairs</b> , +/- <b>cartilage</b>	Accessory digit (nerve bundles; lacks vellus hairs)
Acne keloidalis nuchae	Suppurative folliculitis with mixed inflammation (neutrophils, plasma cells, and lymphocytes), hypertrophic scar, and naked hair shafts	Folliculitis decalvans (similar, but lacks hypertrophic scar), LPP (lymphocytic inflammation; usually lacks free hair shafts)
Acquired digital fibrokeratoma	Polypoid, massive orthohyperkeratosis, and vertically oriented collagen	Wart (koilocytes), accessory digit (nerves)
Actinomyces	Light-colored grains of filamentous bacteria surrounded by Spendore-Hoeppli phenomenon (pink)	Eumycetoma, botryomycosis
AFX	Dense dermal proliferation of spindled cells, histiocyte-like cells, foam cells, and <b>bizarre multinucleated cells</b> ; <b>numerous atypical mitoses</b> ; +/- ulceration	Undifferentiated pleomorphic sarcoma and pleomorphic dermal sarcoma (extend to fat or deeper soft tissue), <b>SLAM DDx</b>
Alopecia areata	<b>"Swarm of bees"</b> lymphocytic infiltrate near hair bulb in fat; shift to catagen/telogen; <b>lymphocytes, eosinophils, and melanin in fibrous tracts</b> (newly reported finding), +/- pigment casts	Trichotillomania (has pigment casts, but also has trichomalacia; lacks eosinophils and lymphocytes in fibrous streamer tracts), lichen planopilaris (inflammation much more superficial [infundibulum])
Amalgam tattoo	<b>Oral mucosa</b> , dark colored specks along BMZ and scattered throughout dermis (in macrophages or along elastic fibers)	Normal skin DDx
Amyloid (macular and lichen)	Waxy pink globules in papillary dermis, pigment incontinence, and <b>amyloid is keratin-derived (AK)</b>	Normal skin DDx, colloid milium (extends deeper into dermis; adult form has prominent solar elastosis); nodular amyloid (deeper, ↑inflammation w/ plasma cells, and amyloid is light-chain derived = AL)
Amyloid (nodular)	Large fissured pale pink material in superficial and <b>deep</b> dermis, prominent inflammation w/ <b>plasma cells</b> , and <b>amyloid is light chain-derived (AL)</b>	Macular/lichen amyloid (more superficial, keratin-derived, and lacks inflammation), colloid milium (lacks inflammation)
Angiofibroma (fibrous papule, Koenen tumor, and adenoma sebaceum)	Papule, proliferation of normal and stellate fibroblasts w/ <b>concentric perivascular fibrosis</b>	DF (collagen trapping, epidermal hyperplasia)
Angiolipoma	Lipoma w/ lobular capillary proliferations +/- intravascular thrombosis	Lipoma (lacks proliferative collections of capillaries), spindle cell lipoma (myxoid stroma w/ small spindle cells, "ropey" bright pink collagen, lacks capillary proliferations)
Angiosarcoma	Poorly circumscribed dermal proliferation of anastomosing vessels; atypical, plump, <b>hyperchromatic</b> endothelial cells with <b>multi-layering, mitoses</b>	Kaposi (cells are <b>spindled</b> and not nearly as hyperchromatic nor as mitotically active; slit-like vessels, hemorrhage, <b>plasma cells</b> , promontory sign), and aneurysmal DF (peripheral collagen trapping; giant cells containing hemosiderin)
Arteriovenous malformation (AV hemangioma)	<b>Mix of thick</b> (centrally located) and <b>thin</b> (peripherally located) walled vessels in mid-upper dermis	Lobular capillary hemangioma (small thin-walled capillaries and endothelial cells), angioleiomyoma (located much deeper in SQ; concentric pink smooth muscle compresses large vessels to form slit-like vessels)
Balloon cell nevus	Melanocytes w/ abundant vacuolated clear cytoplasm, dermal melanophages, and scattered conventional nevus nests	Renal cell carcinoma (very vascular w/ hemorrhage; lacks dermal melanophages), clear cell hidradenoma (sweat ducts; foci of keratinizing dermal nests), xanthoma (lacks pigment and junctional nests)

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Blastomycosis	<b>PEH w/ intraepidermal pustules</b> , dermal granulomatous inflammation, large 8–15 µm round yeast w/ <b>broad-based budding</b>	Coccidioidomycosis (much larger spherules with endosporeulation; lacks broad-based budding), PEH with pus DDx
Bowen's disease	<b>"Wind-blown"</b> architecture, full-thickness atypia, and <b>dyskeratotic k'cytes</b>	Paget's/EMPD (mucin, nests compress basal keratinocytes), melanoma (pigment, lacks dyskeratotic keratinocytes), MF (lacks dyskeratotic k'cytes, less cytologic atypia)
Branchial cleft cyst	Epidermoid or ciliated pseudostratified cyst lining; <b>prominent lymphoid aggregates w/ germinal centers</b> surrounding cyst	Bronchogenic cyst (smooth muscle and cartilage around cyst; abundant goblet cells), thyroglossal cyst (pink hyaline thyroid follicles)
Bronchogenic cyst	Ciliated columnar/pseudostratified epithelium, <b>goblet cells</b> , smooth muscle and <b>cartilage</b> around cyst	Branchial cleft cyst (prominent lymphoid nodules/germinal centers), thyroglossal cyst (pink thyroid follicles), and cutaneous ciliated cyst (lacks smooth muscle and cartilage)
Bullous impetigo	<b>Superficial acantholysis</b> (PF-like), subcorneal neutrophilic microabscesses +/- bacteria	Pemphigus foliaceus (lacks bacteria and subcorneal neutrophilic microabscesses; positive DIF)
Bullous pemphigoid/herpes gestationis	<b>Sub-epidermal blister w/ eos</b> , eosinophilic spongiosis, and <b>DIF+ (linear IgG and C3 along BMZ)</b>	PCT (pauci-inflammatory, sun-damaged skin), EBA (pauci-inflammatory +/- scattered neuts), bullous EM (apoptotic k'cytes, lymphocytic, eos uncommon), LABD/DH (neutrophils)
Bullous SLE	<b>Sub-epidermal blister w/ neuts</b> , dermal PV/PA lymphocytic inflammation, ↑mucin, and <b>DIF+ (granular to linear IgG (+/- IgA and IgM) along BMZ)</b>	PCT (pauci-inflammatory, sun-damaged skin), EBA (more pauci-inflammatory), bullous EM (apoptotic k'cytes, lymphocytic, eos uncommon), LABD/DH (neutrophilic papillitis)
Calcinosis cutis	Large purple deposits	PXE (small, wavy calcified fibers), calcified pilomatricoma or epidermoid cyst (epithelium surrounds calcified material)
Calciophylaxis	<b>Calcification of small to medium sized vessels w/ thrombosis</b> , extra-vascular calcification, +/- ulceration	Thrombotic vasculopathies (lacks intravascular calcification)
Cellular blue nevus	Highly cellular, purely dermal proliferation of plump or fusiform pale gray melanocytes containing minimal pigment + admixed dendritic melanocytes resembling common blue nevus cells; bulges into subcutis ( <b>"dumbbell configuration"</b> )	Deep penetrating nevus (usually has <b>junctional component</b> and superficial <b>dermal nests resembling ordinary nevus nests</b> (CBN always lacks both of these features!))
Cellular neurothekeoma	Dermal nests and fascicles of spitzoid to histiocytoid appearing cells, S100–, <b>S100A6+</b> , <b>NKI-C3+</b> , and <b>PGP9.5+</b>	"Neurothekeoma"/nerve sheath myxoma (nodules are much less cellular and much more myxoid, cells are S100+ and spindled/fibroblast-like rather than epithelioid/spitzoid)
Chondrodermatitis nodularis helices (CNH)	Central ulceration w/ adjacent epidermal hyperplasia, subjacent healing skin changes, and degenerating (eosinophilic) cartilage	SCC and AK (atypia)
Chromoblastomycosis	<b>PEH + clusters of pigmented round yeast ("copper pennies/medlar bodies")</b> within granulomatous dermal infiltrate	Blastomycosis (also has PEH, but has broad-based budding; lacks brown pigmentation), Phaeohyphomycosis (pigmented hyphae rather than round yeast)
Clear cell acanthoma	<b>Psoriasiform</b> hyperplasia with <b>clear (glycogenated) cells</b> , intracorneal neutrophils, <b>sharp demarcation</b> from surrounding normal skin	Trichilemmoma (large endophytic lobules rather than psoriasiform, peripheral palisading, and thickened pink BMZ), psoriasis (lacks clear cells and is not as sharply demarcated)
Clear cell hidradenoma	Mixture of clear cells, keratinizing cells, sweat ducts, and focal epidermal connection	Balloon cell nevus (dermal melanophages, lacks keratinizing cells, and lacks ducts), renal cell carcinoma (more vascular w/ hemorrhage; lacks keratinizing foci and sweat ducts)
Clonal SK	Whorled intraepidermal nests of k'cytes within SK	Hydroacanthoma simplex (sweat ducts w/ eosinophilic cuticle; smaller monotonous poroid cells), SCCIS (atypical cytology w/ mitoses, dyskeratotic k'cytes, and "windblown" pattern)
Coccidioidomycosis	<b>Large spherules (up to 80 µm)</b> containing smaller endospores	Rhinosporidiosis (gigantic sporangia with central dot-like nuclei and many endospores), blastomycosis (PEH more common; smaller organisms without endospores)
Coma blister	<b>Paucicellular/noninflammatory subepidermal bulla</b> , diffuse epidermal necrosis, and <b>sweat gland necrosis</b>	SJS/TEN (scattered eos; sweat gland necrosis less common)

Continued



**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Congenital nevus	Usually compound nevus with extension down adnexae; melanocytes become singly distributed between collagen in deep dermis	Acquired nevi (do not extend as deeply and do not involve adnexal structures as much)
Cryoglobulinemia type 1	Noninflammatory <b>intravascular occlusion w/ pink PAS+ material in lumen</b>	LCV (vessels destroyed, fibrin in vessel walls rather than occluding lumens)
Cryptococcus	<b>Clear gelatinous capsule (mucicarmine+)</b> surrounding yeast clusters; entire dermis may be gelatinous appearing ("gelatinous Cryptococcus")	Histoplasmosis (much smaller organism, intracellular within histiocytes, and has a pseudocapsule rather than a true capsule)
Cylindroma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Darier disease	Acantholytic dyskeratosis, corps ronds, corps grains	Pemphigus (lacks dyskeratosis, corps ronds/ grains), warty dyskeratoma (more endophytic, more circumscribed lesion)
Deep penetrating nevus	Typically <b>compound</b> , w/ small junctional component, <b>superficial dermal nests resembling ordinary nevus nests</b> , and dense wedge-shaped dermal component of plump epithelioid pigmented melanocytes with abundant melanophages extending into deep dermis/subcutis, tracks along adnexal and neurovascular structures; may have "dumbbell configuration" like CBN	Cellular blue nevus (never has junctional component, never has superficial dermal nests resembling ordinary nevus nests; melanocytes are smaller and much less pigmented), nodular melanoma (severe cytologic atypia w/ mitoses)
Dermal melanocytosis (nevus of Ito/ Ota/Mongolian spot)	Paucicellular, spindled dendritic melanocytes scattered randomly in dermis; <b>lacks dermal sclerosis</b>	Blue nevus (more cellular, surrounding dermal sclerosis); drug-induced hyperpigmentation
Dermatitis herpetiformis	Abscess-like <b>neutrophil aggregates in dermal papillae</b> , small subepidermal bullae, and <b>DIF+ (granular IgA in dermal papillae)</b>	BP (eosinophils predominate, bigger bullae), bullous SLE (lymphocytic and neutrophilic inflammation along DEJ and around adnexae, increased mucin), and LABD (neutrophilic infiltrate and blisters are more diffuse along DEJ; DIF easily distinguishes)
Dermatofibroma	Interstitial "fibrohistiocytic" infiltrate in mid-deep dermis, <b>collagen trapping</b> (best seen at periphery), follicular and epidermal <b>induction</b> , and Touton giant cells containing hemosiderin; <b>Factor XIIIa+, Stromelysin 3+, CD34–</b>	DFSP (infiltrates fat deeply (honeycombing), lacks follicular and epidermal induction, lacks giant cells with hemosiderin; stains: CD34+, factor XIIIa-, and stromelysin 3-)
Dermatofibroma (aneurysmal variant)	DF with abundant hemorrhage and hemosiderin within giant cells; collagen trapping seen at periphery	Angiosarcoma (lacks multinucleate giant cells and collagen trapping), Kaposi sarcoma (lacks multinucleate giant cells)
Dermatofibrosarcoma protuberans (DFSP)	Dense, monomorphous spindle cell proliferation, <b>storiform</b> pattern, extensive <b>honeycombing of fat</b> , <b>CD34+</b> , factor XIIIa-, and stromelysin 3-	Cellular DF (abuts, but does not deeply penetrate fat; peripheral collagen trapping, folliculo-epidermal induction, and hemosiderin-laden multinucleate giant cells), diffuse NF (may also be CD34+ but less densely cellular, lacks honeycombing, and is S-100+)
Dermatomyositis	<b>Subtle vacuolar interface</b> , BMZ thickening, <b>very abundant mucin</b> , and mild inflammation	Lupus (more robust interface changes, less mucin, dense superficial and deep PV/PA lymphocytic inflammation), GVHD (chemotherapy effect common, lacks mucin), EM (more robust interface, lacks mucin)
Digital mucous cyst	Circumscribed nodule of mucin on acral skin	Mucocele (mucosal location), "neurothekeoma" (multiple small nodules of mucin + spindled cells)
Dysplastic nevus	Junctional or compound nevus with at least one of the following: <b>asymmetry</b> , <b>poor circumscription</b> , focal pagetoid scatter, <b>bridging</b> of melanocyte nests, <b>"shouldering"</b> of junctional component, concentric or lamellar <b>papillary dermal fibrosis</b> , and <b>cytologic atypia</b>	Melanoma (diffuse pagetoid scatter, consumption of epidermis, severe cytologic and/or architectural atypia, and lacks of maturation with depth)
Elastosis perforans serpiginosa (EPS)	Narrow, <b>serpiginous</b> epidermal channel w/ perforating <b>pink-red elastic fibers</b>	Reactive perforating collagenosis (thicker volcano-like channel and perforating basophilic collagen)
Endometriosis (cutaneous)	Multiple <b>bland-appearing glands</b> with surrounding <b>edematous/fibromyxoid stroma; hemorrhage</b>	Metastatic adenocarcinoma (lacks fibromyxoid stroma and glandular cells appear malignant)
Epidermodysplasia verruciformis	Pale <b>gray-blue color</b> of upper epidermis	Verruca plana (superficial hypergranulosis w/ clumpy keratohyaline granules +/- koilocytes; lacks pale gray-blue hue), nutritional deficiency (upper half of epidermis is pale/clear colored; psoriasiform hyperplasia)
Epidermolytic hyperkeratosis	<b>Verrucous</b> surface, marked <b>hyperkeratosis</b> , <b>coarse keratohyaline</b> granules, and <b>epidermolysis</b> (k'cytes being ripped apart from each other – can see stretched out spinous connections)	Wart (koilocytes; lacks epidermolysis), acantholytic disorders (keratinocytes rounded, lack spinous connections)

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Epithelioid hemangioma/ALHE	Domed papule, large superficial dermal vessels w/ <b>large epithelioid endothelial cells, dense lympho-eosinophilic infiltrate</b>	G. faciale (infiltrate has neutrophils and plasma cells, not dome shaped, and lacks epithelioid endothelial cells), bug bite/DHR (no increased vessels), Kimura disease (much deeper; not usually tested)
Eruptive xanthoma	Foamy/xanthomatized histiocytes, <b>extracellular lipid</b>	GA (mucin, altered collagen, lacks xanthomatized histiocytes), xanthelasma (eyelid skin, lacks extracellular lipid)
Erythema annulare centrifugum	<b>Tight (“coat-sleeve”)</b> lymphocytic perivascular inflammation +/- mild spongiotic dermatitis	Tumid lupus (abundant mucin +/- vacuolar interface), PMLE (massive papillary dermal edema), DHR (abundant eos)
Erythema induratum/nodular vasculitis	<b>Lobular and septal fat necrosis</b> , granulomatous inflammation (“infection-like”), and <b>vasculitis of medium-sized vessels</b> (“PAN-sized vessels”)	PAN (targets vessels almost exclusively, with minimal fat necrosis)
Erythema multiforme	<b>Basket-weave</b> corneum, <b>scattered necrotic keratinocytes in all levels</b> of epidermis, lymphocyte-predominant, and generally lacks eosinophils	SJS/TEN (diffuse epidermal necrosis, less inflammatory, and more eos), LP (orthohyperkeratosis, epidermal acanthosis, and necrotic k'cytes confined to basal layer), lupus (deeper PV/periadnexal infiltrate, mucin), DM (less k'cyte apoptosis, abundant mucin), GVHD (less inflammatory, epidermal chemo effect/dysmaturation)
Erythema nodosum	<b>Thickened SQ septae</b> w/ granulomatous inflammation, giant cells, and <b>Miescher's granulomas</b>	Lobular panniculitides (involves lobules), eosinophilic fasciitis and deep morphea (may have thickened septae, but lack granulomatous inflammation)
Fibrofolliculoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Fixed drug eruption	<b>EM-like</b> epidermal changes + <b>eosinophils</b> + <b>deeper pigment incontinence</b>	EM (lacks: eosinophils and deep pigment incontinence; lymphocyte predominant), SJS/TEN (less inflammatory), GVHD (lacks eosinophils; more adnexal interface)
Follicular mucinosis (alopecia mucinosa)	<b>Mucin in follicle</b> +/- adnexotropic atypical lymphocytes; conspicuous eosinophils	Follicular eczema (spongiosis in follicles; lacks mucin)
Folliculitis decalvans	<b>Suppurative folliculitis</b> w/ mixed inflammation (neutrophils, plasma cells, and lymphocytes), free hair shafts	LPP (lymphocytic inflammation, typically lacks free hair shafts), acne keloidalis nuchae (similar, but has hypertrophic scar)
Giant cell tumor of tendon sheath	Dense proliferation of <b>osteoclastic giant cells</b> and histiocytes, located very deep (near tendon)	JXG (more superficial (dermis), has Touton giant cells and xanthomatized histiocytes; lacks osteoclastic GCs), giant cell epulis (oral equivalent of GCTTS)
Glomus tumor	Dermal proliferation of monotonous round blue cells w/ associated vessels	Mastocytoma (“fried egg” mast cells, more abundant cytoplasm, and lacks vascular component), poroma/dermal duct tumor (sweat ducts; lacks vessels w/ RBCs)
Gout	<b>Needle-shaped crystals</b> w/ surrounding granulomatous inflammation	Intralesional kenalog deposits (amorphous, bubbly foreign material, rather than needle-shaped)
Granular cell tumor	Dermal proliferation of cells w/ granular cytoplasm and <b>pustuloovoid bodies</b> of Milian, <b>pseudoepitheliomatous hyperplasia</b> (50%), <b>S100+</b>	Hibernoma (deeper, large intracytoplasmic vacuoles), xanthoma (foamy histiocytes are whiter, vs. pink cytoplasm in GCT), SCC
Granuloma annulare (classic type)	Distinct zones of palisaded histiocytes encircling altered collagen and mucin; areas of normal intervening dermis; frequent eosinophils	NLD (square biopsy sign, diffuse/pan-dermal necrobiosis (degenerated collagen), plasma cells, and lacks eosinophils), Rheumatoid nodule (deeper, central pink fibrin rather than mucin, and neutrophilic debris), AEGCG (elastophagocytosis, focal loss of solar elastosis), epithelioid sarcoma (pseudo-palisaded w/ central tumor necrosis and atypical peripheral cells w/ mitoses)
Granuloma annulare (interstitial)	Interstitial histiocytes w/ adjacent <b>mucin</b> , mild collagen degeneration, and PV lymphoeosinophilic inflammation	Kaposi sarcoma (spindled cells, hemorrhage, hemosiderin, and abundant plasma cells; lacks mucin), metastatic breast carcinoma (atypical cells w/ small duct formation; lacks mucin), leukemia cutis/AML (immature neutrophils/band forms, atypical myeloblasts w/ mitoses; no mucin and no collagen alteration)
Granuloma faciale	<b>Grenz zone</b> ; perivascular mixed inflammation ( <b>neutrophils, plasma cells, eosinophils</b> , and lymphocytes)	ALHE/epithelioid hemangioma (dome-shaped, large epithelioid endothelial cells, infiltrate predominantly lymphocytes and eosinophils; much less neutrophils and plasma cells), EED (similar to GF, but has “onion skin” vessel thickening)

Continued

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Guttate psoriasis	<b>Thick, mounded parakeratosis adherent</b> to epidermis; neutrophilic microabscesses	Pityriasis rosea (thinner, nonadherent mounds of parakeratosis, RBC extravasation, and lacks neuts)
GVHD	Vacuolar (> lichenoid) interface, sparse lymphocytic infiltrate, <b>“CHEMO effect”</b> (dysmaturation of k'cytes), and <b>“satellite cell necrosis”</b> (apoptotic k'cytes abutting lymphocytes)	EM (more inflammatory), DM (more mucin), and lupus (dense superficial and deep PV/PA inflammation)
Hailey-Hailey	<b>Epidermal hyperplasia</b> (acanthosis), acantholysis ( <b>“dilapidated brick wall”</b> ), and <b>k'cytes appear pinker</b> than normal	Darier's (more corps ronds/grains), Pemphigus (lacks acanthosis, involves follicles, tombstoning, and DIF+)
Halo nevus	Dense lymphocytic infiltrate mingling with nevus cells ( <b>“Cocktail party”</b> )	Melanoma w/ lichenoid regression (band-like lymphocytic infiltrate deep to melanoma, less mingling → “riot police”) and LP (lacks nevus)
Hibernoma	Eosinophilic lipocytes w/ multivacuolated <b>“mulberry cells”</b>	Granular cell tumor (more superficial – dermis, smaller cells, and pustulovoid bodies of Milian)
Hidradenoma (nodular hidradenoma and eccrine acrospiroma)	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Hidradenoma Papilliferum	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Hydroacanthoma simplex (intraepidermal poroma)	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Hidrocystoma	Simple cyst with two cell layer thick lining (apocrine or eccrine)	Steatocystoma (eosinophilic “shark tooth” lining and sebaceous glands in cyst wall) and PEA/TAA (multiple smaller cysts +/- papillary projections)
Histoplasmosis	Granulomatous inflammation with <b>parasitized histiocytes</b> containing small 2–3 µm dots <b>evenly spaced</b> throughout cytoplasm; each organism has <b>pseudocapsule</b> ; narrow-based unequal budding	Leishmaniasis (“marquee sign,” kinetoplast, and lacks pseudocapsule)
HSV/VZV	<b>Acantholysis</b> , viral cytopathic changes ( <b>M</b> ultinucleated k'cytes, chromatin <b>M</b> argination, nuclear <b>M</b> olding, and steel-gray k'cytes)	Pemphigus (lacks multinucleated cells and viral cytopathic changes)
Hyalohyphomycosis (Aspergillus, Fusarium and Penicillium)	<b>Narrow, septated, blue hyphae</b> with <b>bubbly cytoplasm</b> , <b>45° branching</b> ; <b>angioinvasive</b> with subsequent thrombosis and epidermal/dermal necrosis	Zygomycosis (broad, nonseptated, pink hollow hyphae with 90° branching, angioinvasive – epidermal/dermal necrosis)
Ichthyosis vulgaris	<b>Compact orthohyperkeratosis</b> w/ paradoxically decreased granular <b>layer</b>	Normal skin DDx
Incontinentia pigmenti	Eosinophilic spongiosis; <b>apoptotic k'cytes</b> (most helpful clue to DDx)	Allergic contact dermatitis (“flask-shaped” Langerhans cell microabscesses; lacks apoptotic k'cytes), bullous pemphigoid (eosinophils line up at DEJ, subepidermal bullae, and lacks apoptotic k'cytes)
Infantile digital fibromatosis	Dome-shaped nodule; fascicles of <b>spindled myofibroblasts</b> w/ characteristic perinuclear eosinophilic cytoplasmic <b>inclusion bodies</b>	Scar (lacks inclusions), digital fibrokeratoma (lacks spindle cells w/ eosinophilic inclusions)
Intravascular papillary endothelial hyperplasia (Masson's tumor, IPEH)	<b>Sharply circumscribed</b> , reorganizing thrombus within large vessel; papillary projections	Kaposi (infiltrative architecture, poorly circumscribed; lacks thrombus), angiosarcoma (very atypical hyperchromatic endothelial cells, mitoses)
Inverted follicular keratosis	Endophytic version of irritated SK (squamous eddies; minimal cytologic atypia; smooth tumor base)	SCC (cytologic atypia; infiltrative deep border)
Juvenile xanthogranuloma (JXG, xanthogranuloma)	Domed nodule, dense histiocytic infiltrate w/ <b>Touton giant cells</b> , foam cells, and <b>eosinophils</b>	Reticulohistiocytoma (two-toned cytoplasm, less xanthomatized/Touton cells) and xanthoma/xanthelasma (all xanthomatized histiocytes)
Kaposi sarcoma	Bundles and fascicles of relatively bland spindle cells, <b>thin “sieve-like” vessels</b> w/ hemorrhage, conspicuous <b>plasma cells</b> ; all forms are <b>HHV8+</b>	Angiosarcoma (cells typically round rather than spindled, endothelial cells much more atypical and hyperchromatic w/ ↑mitoses), aneurysmal DF vs nodular KS (cells more atypical, peripheral collagen trapping, and giant cells w/ hemosiderin), interstitial GA vs plaque KS (mucin, collagen alteration; lacks: hemorrhage, hemosiderin, and plasma cells)
Keloid	Large, haphazardly arrayed, thick red collagen bundles; acellular stroma	Scar (more fibroblastic, horizontal collagen orientation, smaller collagen bundles)
Keratin granuloma	Thin <b>flecks of keratin</b> surrounded by <b>foreign body giant cells</b> +/- cholesterol clefts	None

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Langerhans cell histiocytosis	Aggregates of <b>reniform cells</b> floating in edematous papillary dermis +/- epidermotropism,	MF (hyperchromatic lymphoid cells w/ minimal cytoplasm, less edema), mastocytosis ("fried egg" cells)
LCV	Perivascular <b>neutrophilic infiltrate</b> w/ <b>leukocytoclasia, fibrin deposition, vascular damage</b> , and RBC extravasation	Urticaria (lacks RBC extravasation, vessel damage, and leukocytoclasia), Sweet's syndrome (neutrophilic infiltrate way more diffuse; massive papillary dermal edema)
Leiomyoma (angioleiomyoma)	SQ nodule, concentric nodules of smooth muscle <b>encircling collapsed/"slit-like" vessels</b>	Piloileiomyoma (more superficial, haphazardly arrayed fascicles of smooth muscle; lacks vascular component)
Leiomyoma (piloileiomyoma)	Circumscribed dermal nodule, haphazardly arrayed fascicles of pink smooth muscle resembling arrector pili, cigar-shaped nuclei, and clear perinuclear vacuoles	Angioleiomyoma (deeper – arises in SQ, concentric nodules of smooth muscle encircling collapsed/"slit-like" vessels), smooth muscle hamartoma, and Becker's nevus (smaller muscle bundles, hyperpigmented and papillomatous epidermis)
Leishmaniasis	Granulomatous inflammation with <b>parasitized histiocytes</b> containing 2 µm dots <b>around periphery</b> ("marquee sign"), <b>kinetoplast</b>	Histoplasmosis (organisms more evenly spaced throughout cytoplasm and have pseudocapsules)
Leprosy (lepromatous)	<b>Grenz zone</b> ; perivascular lymphohistiocytic inflammation; globi	Grenz zone DDx (G. faciale, leukemia cutis, and cutaneous B-cell lymphoma)
Leprosy (tuberculoid)	Horizontal/linear <b>granulomas tracking along nerves</b>	Lepromatous leprosy (Grenz zone; perivascular lymphohistiocytic inflammation; globi), sarcoidosis (lacks horizontal granulomas)
Leukemia cutis (AML, AMML)	<b>Grenz zone</b> ; "Indian-file" infiltrate of immature neutrophils, band forms and atypical myeloid cells/myeloblasts	Metastatic breast carcinoma (larger cells, forms ducts), interstitial GA (mucin, collagen alteration)
Lichen nitidus	<b>"Ball and claw"</b> (downward projections of epidermis encircle lichenoid-granulomatous infiltrate), atrophic overlying epidermis	LP (lacks granulomatous component, less circumscribed)
Lichen planopilaris	Dense lymphocytic inflammation w/ follicular interface centered around infundibulum, lacks interfollicular epidermal interface, and lacks deep PV/PA inflammation	DLE (interfollicular + follicular interface centered deeper (isthmus), mucin, and denser superficial and deep PV lymphocytic inflammation), folliculitis decalvans (mixed (neuts and plasma cells) infiltrate without interface)
Lichen planus	<b>Orthohyperkeratosis</b> , wedge-shaped <b>hypergranulosis</b> , "sawtoothed rete," apoptotic k'cytes localized to basal layer, lichenoid infiltrate, and lacks eos (except hypertrophic LP and drug-induced LP)	Lupus (less lichenoid, infiltrate extends deeper, and increased mucin), GVHD (less inflammatory, chemo-effect), EM (less lichenoid, apoptotic k'cytes scattered in all levels), and drug-induced LP (parakeratosis, eosinophils present)
Lichen planus (drug)	Like LP, but has parakeratosis, <b>eosinophils</b>	LP (lacks parakeratosis and eosinophils)
Lichen planus (oral)	Like LP, but has <b>parakeratosis; lacks granular layer</b>	LP (hypergranulosis, lacks parakeratosis), syphilis (dirty infiltrate [neuts, plasma cells, and debris])
Lichen planus-like keratosis ("benign lichenoid keratosis")	Like LP, but solitary, +/- parakeratosis and eosinophils	LP (lacks parakeratosis and eosinophils)
Lichen sclerosis (LS&A)	<b>Orthohyperkeratosis</b> , edematous-hyalinized <b>superficial dermis</b> w/ dense underlying lichenoid lymphocytic infiltrate; follicular plugging	Radiation dermatitis (entire dermis appears hyalinized "sick"; noninflammatory)
Lichen simplex chronicus	Orthohyperkeratosis, <b>hypergranulosis, irregular epidermal hyperplasia</b> , and papillary dermal fibrosis (vertical collagen)	Psoriasis (parakeratosis, regular "psoriasiform" epidermal hyperplasia), prurigo nodularis (on spectrum, but more dome shaped)
Lichen striatus	LP-like interface at DEJ + <b>peri-eccrine</b> inflammation	LP (lacks peri-eccrine infiltrate), pemio (dermal edema; lacks prominent interface)
Linear IgA dermatosis/chronic bullous disease of childhood	Similar to DH, but <b>more confluent</b> dermal neutrophilic inflammation and <b>larger bullae</b> , DIF+ (linear IgA along BMZ)	DH and bullous SLE (DIF easily distinguishes)
Lipodermatosclerosis	Lipomembranous fat necrosis (" <b>frost on window pane</b> "), dermal and pannicular fibrosis, +/- <b>stasis</b> changes	Lupus panniculitis/profundus (may have lipomembranous changes but also has dense PV inflammation and mucin)
Livedoid vasculopathy (atrophie blanche)	Thick pink fibrin (" <b>pink-red crayon</b> ") deposition in vessel walls	LCV (more inflammatory w/ perivascular neutrophilic infiltrate, vessel destruction and leukocytoclasia); PCT (cell-poor subepidermal bulla)
Lobomycosis	Numerous large organisms linked together in chains (" <b>pop bead-like</b> "), granulomatous infiltrate	Blastomycosis (similar size, but does not form long chains)
Lobular capillary hemangioma (pyogenic granuloma)	Polypoid or nodular, <b>lobular proliferation of endothelial cells</b> and small capillary-sized vessels, noninfiltrative architecture, +/- ulceration	Bacillary angiomatosis (similar, but has abundant neutrophils and clumps of bacteria), angiosarcoma (infiltrative rather than lobular; atypical hyperchromatic endothelial cells w/ atypical mitoses)

Continued



**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Lupus (discoid)	<b>Orthohyperkeratosis</b> , vacuolar-to-lichenoid interface dermatitis of hair follicles (> interfollicular epidermis), dilated follicles w/ follicular <b>keratin plugs</b> , superficial and deep PV/PA lymphoplasmacytic infiltrate, and <b>↑mucin</b>	SCLE (more basal vacuolar change, epidermal atrophy and superficial mucin; less orthohyperkeratosis, dermal inflammation, follicular plugging, and BMZ thickening), LPP (interfollicular epidermis not involved; lacks PV inflammation, mucin and follicular plugging)
Lupus (SCLE)	Orthohyperkeratosis, prominent basal vacuolar interface, epidermal atrophy, superficial mucin, mild superficial and deep PV/PA lymphocytic inflammation	DLE (more dermal PV/PA lymphocytic inflammation, interface changes most prominent at follicles, follicular plugging, less basal vacuolar change), DM (less interface, less inflammation, much more mucin), EM (basket weave stratum corneum, lacks deep PV/PA inflammation and mucin), GVHD (chemotherapy-induced epidermal dysmaturation, less deep PV/PA inflammation, lacks mucin), and FDE (basket weave corneum, more eosinophils and pigment incontinence lacks mucin)
Lupus (tumid)	<b>Massively increased dermal mucin</b> (rivaling DM), moderately dense superficial and deep PV/PA lymphocytic inflammation	Jessner's lymphocytic infiltrate (lacks mucin), DM (subtle vacuolar interface, lacks significant dermal PV/PA inflammation)
Lupus profundus/panniculitis	<b>Hyaline lobular fat necrosis</b> ("pink wax" appearance), <b>nodular lymphoid aggregates w/ plasma cells</b> , interface changes (20%–50%), +/- mucin, +/- lipomembranous changes	Gamma-delta T-cell lymphoma (fat rimming, atypical lymphocytes, lacks nodular lymphoid aggregates and plasma cells), SPTCL (fat rimming, lacks interface, and lacks nodular lymphoid aggregates)
Lymphangioma	Pink lymphatic fluid within widely ectatic lymphatic vessels w/ intraluminal valves	Venous lake (RBCs within solitary ectatic vessel; lacks valves)
Lymphomatoid papulosis	Dense <b>wedge-shaped</b> infiltrate w/ <b>neutrophils, eosinophils, and large CD30+ Reed-Sternberg-like cells</b> ; +/- RBC extravasation; lichenoid interface and ulceration	PLEVA (purely lymphocytic, lacks eosinophils), ALCL, and MF w/ large cell transformation (need clinical history)
Mastocytoma	Aggregates of monomorphous <b>"fried egg" mast cells</b>	Intradermal nevus (lacks fried egg cells, cells are nested), glomus tumor (vessels present, cells have less cytoplasm)
Melanoma (lentigo maligna type)	<b>Poorly circumscribed lentiginous (single cell) proliferation</b> of melanocytes along DEJ and follicular epithelium, arises on <b>solar elastotic skin</b> , variability of melanocyte nest size and shape, pagetoid scatter (less than superficial spreading type), variable degrees of cytologic atypia	Pagetoid DDx (see Table 7-22)
Melanoma (superficial spreading type)	Asymmetric, poorly circumscribed, often trails off as single junctional cells rather than nests, <b>epidermal consumption/thinning</b> , <b>pagetoid scatter</b> diffuse throughout lesion, severe cytologic atypia (enlarged irregular nuclei, prominent <b>"cherry red" nucleoli</b> ), increased mitotic rate, and lacks maturation with depth	Spitz nevus (symmetric, well-circumscribed, begins and ends in nests, spindled and epithelioid melanocytes with enlarged amphophilic or pink cytoplasm, "raining down" pattern of nests and cells, clefts around junctional nests, epidermal hyperplasia rather than consumption/thinning, Kamino bodies, maturation with depth, and pagetoid scatter limited to central portion of lesion) Pagetoid DDx (see Table 7-22) Dysplastic nevus (bridging of melanocyte nests, "shouldering" of junctional component beyond dermal component, concentric or lamellar papillary dermal fibrosis, cytologic atypia; distinguished from melanoma mainly by ABSENCE of diffuse pagetoid scatter, severe cytologic atypia, or consumption of epidermis)
Merkel cell carcinoma	Dense basaloid infiltrate (low power), pale/"washed-out" blue nuclei with <b>"salt and pepper" chromatin</b> (high power), nuclear molding, innumerable mitoses, <b>CK20+ (dot-like/perinuclear)</b> , and TTF-1-	Metastatic small cell lung cancer (TTF-1+ and CK20-); lymphoma (nuclei more basaloid/hyperchromatic on high power)
Metastatic breast adenocarcinoma	Infiltrative single cells (" <b>Indian filing</b> ") and <b>small glands</b> with <b>cytologic atypia</b> , mitoses and apoptosis, +/- <b>intralymphatic tumor clusters</b>	Interstitial GA (mucin, altered collagen, lacks atypia and glands), leukemia cutis (often see associated neutrophils, immature myeloid cells and "band forms"; lacks gland formation), malignant primary cutaneous adnexal carcinomas (p63+ and CK5/6+, unlike metastatic adenocarcinomas)
Metastatic colon adenocarcinoma	Infiltrative glands with cytologic atypia, mitoses and tumor necrosis (" <b>dirty necrosis</b> ")	Endometriosis (larger glands lacking atypia, fibromyxoid or edematous stroma surrounds glands), malignant primary cutaneous adnexal neoplasms (p63+ and CK5/6+, unlike metastatic adenocarcinomas)

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Metastatic renal (clear) cell carcinoma	Dense pan-dermal proliferation of clear cells; <b>highly vascular</b> lesion with dermal hemorrhage	Clear cell hidradenoma (contains squamoid cells, sweat ducts, and a hyalinized/keloidal collagenous stroma), balloon cell nevus (can always identify conventional nevus nests elsewhere in lesion, melanophages, lacks hemorrhage and increased vascularity)
Microcystic adnexal carcinoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Mixed tumor (chondroid syringoma)	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Morpheaform BCC	Angulated strands and islands of atypical basaloid cells, clefting, numerous apoptoses and mitoses	Desmoplastic trichoepithelioma (small tadpole/"paisley tie"-shaped basaloid epithelial islands and nests, fibroblast-rich pink stroma, and abundant small horn cysts with calcifications), syringoma (basaloid tadpoles with sweat ducts containing eosinophilic cuticle and amorphous pink sweat; sclerotic stroma; lacks horn cysts and calcifications), MAC (mixed follicular and sweat gland differentiation; extends deeper, perineural invasion and lymphoid aggregates), and syringoma (sweat glands w/ eosinophilic cuticle and amorphous pink sweat, much fewer horn cysts and calcifications)
Mucinous carcinoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Mucocele	Circumscribed nodule of mucin, mucosal location, minor salivary glands present	Digital mucous cyst (acral), nerve sheath myxoma (aka "neurothekeoma," multiple hypocellular dermal nodules comprised of abundant mucin and scattered spindled/fibroblast-like cells)
Mycosis fungoides	<b>Epidermotropism</b> , <b>Pautrier microabscesses</b> , hyperchromatic <b>cerebriform lymphocytes</b> surrounded by halo, superficial band-like lymphocytic infiltrate, <b>"bare underbelly" sign</b> , "wiry" papillary dermal collagen, and minimal spongiosis relative to degree of lymphocytes in epidermis	Melanoma in situ (nested pigmented melanocytes), SCCIS (dyskeratotic k'cytes, solar elastosis), Paget's/EMPD (mucin within nests, ducts), and LCH (reniform cells w/ increased cytoplasm, papillary dermal edema)
Myofibroma/ myopericytoma	<b>Biphasic proliferation</b> : 1) <b>hypocellular</b> areas of blue-pink nodules (may appear cartilaginous, "myoid," or hyalinized) with bland myofibroblasts; 2) <b>hypercellular</b> areas w/ primitive-appearing round, blue cells with ↑N:C ratio, and ectatic <b>"staghorn"/"hemangiopericytoma-like"</b> vessels	Mixed tumor/chondroid syringoma (has sweat ducts, lacks staghorn vessels)
Myxoid liposarcoma	<b>"Chicken wire"</b> blood vessels in myxoid background; scattered lipoblasts	Spindle cell lipoma (resembles lipoma, but has myxoid zones containing bland spindle cells and scattered thick ("ropey") bright pink collagen fibers; lacks lipoblasts, mitoses and "chicken wire" vascular pattern)
Necrobiosis lipidica (NLD)	Square biopsy sign, diffuse <b>"cake-layered" necrobiosis</b> (lacks intervening areas of normal collagen), frequent plasma cells, and lacks eosinophils	GA (focal zones of palisaded necrobiosis w/ <b>intervening areas of normal collagen</b> , has <b>eosinophils</b> ; lacks square biopsy and plasma cells), NXG (cholesterol clefts; large and bizarre-shaped foreign body giant cells; "dirtier" [cellular debris])
Necrobiotic xanthogranuloma	Broad zones of dermal and SQ necrosis + granulomatous inflammation; Touton giant cells, lipidized histiocytes and <b>gigantic multinucleated giant cells</b> (much larger than those seen in NLD) with horseshoe or <b>osteoclastic</b> appearance (up to 50-100 nuclei may be present in a single giant cell!), neutrophilic debris, <b>cholesterol clefts</b> , plasma cells	NLD (fewer cholesterol clefts and foamy histiocytes, lacks the "dirty" neutrophilic debris and bizarre multinucleated giant cells), plane xanthoma (nearly identical appearance)
Nephrogenic systemic fibrosis (NSF and NFD)	↑ <b>CD34+ fibrocytes in dermis and SQ</b> septae, variably thickened collagen fibers, and ↑ <b>dermal mucin</b>	Scleromyxedema (almost identical, but does not extend as deeply into fat), morphea/scleroderma (thick hyalinized collagen, no increase in cellularity, loss of CD34+ dermal fibrocytes, and lacks mucin)
Nerve sheath myxoma ("neurothekeoma")	Multiple small myxoid nodules w/ bland S100+ spindled cells	Angiomyxoma, myxoma, digital mucous cyst, and mucocele (lack multi-nodular architecture)
Neurofibroma	Superficial nodule, <b>haphazard proliferation</b> of wavy spindle cells, pink <b>"bubble gum" stroma</b> , and <b>mast cells</b>	Angioleiomyoma (deep SQ nodule, dense pink smooth muscle cell proliferation w/ cigar-shaped nuclei and perinuclear vacuole, and compressed large vessels w/ slit-like lumens), pili leiomyoma (fascicles of dense pink smooth muscle cells w/ cigar-shaped nuclei and perinuclear vacuole, lacks mast cells), PEN (more sharply circumscribed w/ surrounding pseudocapsule, organized as fascicles rather than haphazard), schwannoma (much deeper SQ nodule, much more organized architecture, Verocay bodies, and large dilated/hyalinized vessels)

Continued

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Nevus sebaceus	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Nodular amyloid	Large amorphous pink dermal nodules; ↑ <b>plasma cells</b>	Macular/lichen amyloid (more superficial, lacks plasma cells), lipid proteinosis (lacks plasma cells)
Nodular fasciitis	<b>Circumscribed</b> nodule in SQ or fascia, <b>“tissue culture-like”</b> fibroblasts in <b>feathery/myxoid stroma</b> , extravasated <b>RBCs</b> , and <b>lymphocytic inflammation</b> ; mitoses are common, but never atypical	Fibrosarcoma (not well-circumscribed, atypical hyperchromatic nuclei with “herringbone” pattern, lacks “feathery” appearance and mucin), low-grade myxofibrosarcoma (characteristic “curvilinear” vessels, atypical hyperchromatic cells), fibromatosis (more uniformly cellular, longer “sweeping” fascicles of fibroblasts/myofibroblasts with wavy nuclei, collagenous rather than myxoid stroma)
Nutritional deficiency (NME and acrodermatitis enteropathica)	<b>Psoriasiform</b> hyperplasia; <b>pallor</b> of superficial epidermis	Psoriasis (lacks epidermal pallor), epidermodysplasia verruciformis (upper epidermis light blue, not pale-white)
Ochronosis	Yellow-brown banana-shaped bodies in dermis	None
Orf	Intraepidermal blister; <b>eosinophilic inclusion bodies</b> in k'cytes	HSV/VZV (acantholysis, multinucleate cells, nuclear molding and chromatin margination)
Osteoma cutis	Pink bone in dermis (purple if calcified)	Calcinosis cutis (purple instead of pink)
Paget's disease/EMPD	Intraepidermal nests of <b>pale bluish cells</b> , compressed basal k'cytes, diffuse pagetoid scatter ( <b>“buckshot”</b> pattern), and transepidermal elimination of tumor cells; <b>CK7+</b> , <b>CK20-</b>	Pagetoid DDx (see Table 7-22)
Palisaded encapsulated neuroma (solitary circumscribed neuroma)	<b>Superficial</b> dermal nodule; sharply circumscribed w/ <b>pseudocapsule</b> ; wavy nuclei and <b>well-organized</b> nerve fascicles	Schwannoma (much deeper (SQ or deeper) and larger, mixture of Antoni A and B areas, Verocay bodies, has true capsule, and large ectatic/hyalinized vessels), NF (less circumscribed, haphazard rather than organized, and lacks fascicles), angioleiomyoma (much deeper SQ nodule, concentric proliferation of pink smooth muscle cells encircle large vessels w/ collapsed “slit-like” lumens), and pilioliomyoma (not sharply circumscribed, cigar-shaped nuclei)
Pancreatic fat necrosis	Calcified necrotic lipocytes ( <b>“ghost cells”</b> )	SQ fat necrosis of newborn and poststeroid panniculitis (maple leaf-shaped crystals within lipocytes + granulomatous inflammation), sclerema neonatorum (maple leaf-shaped crystals within lipocytes)
Paracoccidioidomycosis	Multiple <b>radially distributed</b> round yeast arising from central larger yeast ( <b>“mariner's wheel”</b> ); narrow-based budding	None
Pemphigus erythematosus	Indistinguishable from pemphigus foliaceus on H&E; <b>DIF shows granular to linear deposition along BMZ in addition to intercellular staining</b>	Pemphigus foliaceus (DIF distinguishes)
Pemphigus foliaceus	Superficial acantholysis (granular layer or upper spinous layer), DIF+ (intercellular IgG and C3)	Bullous impetigo (subcorneal neutrophilic microabscesses +/- bacteria), SSSS (need DIF), and pemphigus vulgaris (deeper acantholysis, tombstoning of basal k'cytes)
Pemphigus vegetans	<b>PEH</b> with intraepidermal <b>eosinophilic abscesses</b> /spongiosis; +/- acantholysis	Chromoblastomycosis, blastomycosis, coccidioidomycosis (fungal organisms present in dermal granulomatous areas; lacks eosinophilic abscess and acantholysis), and halogenoderma (neutrophilic abscesses)
Pemphigus vulgaris	<b>Acantholysis, tombstoning</b> of basal k'cytes, follicular acantholysis, DIF+ (intercellular IgG and C3)	Hailey-Hailey ( <b>epidermal hyperplasia</b> , k'cytes appear pinker than normal, scattered dyskeratotic k'cytes, lacks follicular involvement, and DIF negative), pemphigus foliaceus (more superficial acantholysis; lacks tombstoning), HSV/VZV (viral cytopathic changes w/ necrotic k'cytes, interface dermatitis and sebaceitis/sebaceous gland necrosis), IgA pemphigus (subcorneal or intraepidermal neutrophilic microabscesses with minimal-no acantholysis), and paraneoplastic pemphigus (acantholysis + interface dermatitis with apoptotic k'cytes, DIF+ in intercellular and BMZ pattern)
Pernio	<b>Acral</b> skin, papillary dermal edema, dense lymphocytic infiltrate, and peri-eccrine involvement	PMLE (lacks peri-eccrine inflammation, non-acral skin), lupus (less edema, more mucin)
Pigmented purpuric dermatosis	Mild perivascular lymphocytic infiltrate w/ RBC extravasation and dermal <b>pigment (hemosiderin)</b>	Nevus of Ota/Ito (pigmented melanocytes are more diffuse; melanin less refractile)

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Pigmented spindle cell nevus (Reed's nevus)	Same as Spitz nevus except more pigmented, almost entirely comprised of <b>spindle cells</b> , +/- overlying pigmented parakeratosis; has <b>minimal to no dermal involvement</b> (if present, is confined to superficial dermis)	Spitz nevus (mixture of epithelioid and spindle cells, cytoplasm more pink or amphophilic, less pigmented, and has ability to extend deeper into dermis), melanoma (not sharply circumscribed, often trails off as single junctional cells rather than nests, epidermal consumption/thinning, and diffuse pagetoid scatter throughout lesion)
Pilomatricoma	<b>Peripheral basaloid cells</b> , central anucleate <b>"ghost cells,"</b> and <b>calcified debris</b> ; "rolls and scrolls" architecture	Trichilemmal cyst (lacks ghost cells)
Pityriasis rosea	<b>Thin</b> , nonadherent mounds of parakeratosis ("scale is flying away from epidermis"), spongiosis, and <b>extravasated RBCs</b>	Guttate psoriasis ( <b>thicker, adherent mounds</b> of parakeratosis; neutrophilic microabscesses)
Pityriasis rubra pilaris (PRP)	<b>Checkerboard parakeratosis, shoulder parakeratosis, follicular plugging</b> , psoriasiform or irregular acanthosis, thick suprapapillary plates, lacks neutrophils, and <b>focal acantholysis</b>	Psoriasis (confluent parakeratosis, more regular epidermal hyperplasia, thinning of suprapapillary plates, lacks checkerboard and shoulder parakeratosis), seborrheic dermatitis (more spongiotic, lacks checkerboard parakeratosis and follicular plugging)
Pleomorphic lipoma	Spindle cell lipoma variant w/ multinucleated <b>floret cells</b> ("flower-like" arrangement of nuclei)	Spindle cell lipoma (lacks floret cells), liposarcoma (atypical hyperchromatic stromal cells in SQ septae, lipoblasts, and mitoses), pleomorphic fibroma (similar appearing multinucleated stromal cells, but is a superficial dermal process)
PLEVA	<b>Parakeratosis, Lichenoid interface, Extravasated blood, V-shaped ("wedge") dermal lymphocytic infiltrate, and Acute epidermal changes</b> (spongiosis +/- ulceration)	LyP (large, atypical CD30+ cells; more mixed infiltrate w/ neuts and eos), lupus (lacks parakeratosis and RBC extravasation)
PMLE	Dense perivascular lymphocytic infiltrate w/ marked <b>papillary dermal edema</b>	Sweet's syndrome (neutrophilic), lupus (less dermal edema, more mucin), dermal hypersensitivity reaction (eosinophils admixed w/ lymphs), pemphigus (acral skin, infiltrate more diffuse/less angiocentric, peri-ecrine inflammation)
Polyarteritis nodosum (PAN)	Vasculitis affecting an isolated (or a few) medium-sized deep dermal/pannicular arteriole; <b>minimal to no involvement of fat lobules</b> away from affected vessel	Erythema induratum (much more extensive lobular involvement w/ fat necrosis and thickened fibrous septae), LCV (affects more superficial vessels), thrombophlebitis (involves veins, not arterioles)
Porokeratosis	Cornoid lamellae	AK (lacks angled cornoid lamellae)
Poroma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Pretibial myxedema	Abundant <b>mucin</b> concentrated in mid to lower dermis, <b>widely spaced wispy collagen</b> , and no significant increase in fibroblasts	Scleromyxedema and NSF (abundant spindled cells, less mucin), scleredema (milder increase in mucin; mucin more evenly distributed throughout dermis)
Proliferating pilar (trichilemmal) cyst/tumor	Complex cyst w/ "rolls and scrolls" pattern, squamoid epithelium, and central dense pink trichilemmal keratin, <b>lacks granular layer</b>	Pilomatricoma (peripheral cells very basaloid, central anucleate ghost cells, and frequent calcification and/or ossification)
Protothecosis	<b>Morulae</b> ("soccer ball" appearance)	None
Pseudoxanthoma elasticum	Calcified, curly, and purple elastic fibers in dermis ("PXE = Purple Pubes in Dermis")	None
Psoriasis	Confluent parakeratosis, hypogranulosis, regular/psoriasiform hyperplasia, neutrophilic microabscesses (Munro and Kogoj), and thinning of suprapapillary plates	LSC (orthohyperkeratosis, irregular epidermal hyperplasia, and thickened granular layer), PRP (checkerboard parakeratosis, follicular plugging, irregular acanthosis, thickened suprapapillary plates)
Pustular psoriasis	Subcorneal pustule	AGEP (more dermal edema, eosinophils), candida/tinea/impetigo (organisms present)
Radiation dermatitis	<b>"Sick dermis"</b> w/ pale amorphous collagen, dilated vessels (telangiectasias), atypical or stellate ("radiation") fibroblasts	Morphea ("healthy, robust" collagen bundles; lacks atypical fibroblasts and dilated vessels), LS&A (dense lichenoid infiltrate underlying amorphous area, orthohyperkeratosis)
Reactive perforating collagenosis (RPC)	<b>Wide channel ("volcano-like")</b> w/ perforating <b>basophilic collagen</b>	EPS (thinner pink-red elastic fibers, <b>narrow/thin serpiginous channel</b> )
Recurrent nevus	Atypical junctional melanocytic proliferation overlying dermal scar, +/- benign appearing nevus beneath scar	Melanoma (lacks scar and benign nevus underneath scar), epidermolysis bullosa-associated nevi ("EB nevi" have similar histologic appearance; history of EB is required for Dx)

Continued



**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDx
Reticulohistiocytoma	Granulomatous inflammation + histiocytes with <b>two-toned ("amphophilic") cytoplasm</b> , admixed neutrophils	JXG (Touton giant cells, lacks two-toned histiocytes), Spitz nevus (junctional component, pigment, lacks neutrophils)
Rheumatoid nodule	Deep dermal or SQ palisaded granuloma w/ <b>central pink-red fibrin</b> , neutrophilic debris	GA (more superficial, central blue mucin, eosinophils, lacks neutrophilic debris), gout (needle-shaped crystals), epithelioid sarcoma (pseudo-palisaded w/ central tumor necrosis and atypical peripheral cells w/ mitoses)
Rhinoscleroma	Dense pan-dermal plasma cell infiltrate w/ <b>Russell bodies</b> and <b>Mikulicz</b> cells	Lepromatous leprosy (granulomatous inflammation w/ Grenz zone, globi), granuloma inguinale (PEH w/ neutrophilic abscesses, parasitized histiocytes)
Rhinosporeidiosis	<b>Gigantic sporangia</b> (up to 300 µm) with <b>central nucleus</b> and numerous endospores	Coccidioidomycosis (smaller spherules (8–80µm), +/- PEH)
Sarcoidosis	Epithelioid histiocytes aggregate to form <b>"naked granulomas"</b> (minimal surrounding lymphocytic inflammation)	Tuberculoid leprosy (linear granulomas along nerve, more lymphocytic inflammation around granulomas, foreign body granuloma (frequently see polarizable material), granulomatous rosacea (perifollicular), cutaneous Crohn's disease (need CPC), and zirconium/beryllium granulomas (not polarizable – need spectrography)
Scabies	Mite in subcorneal area; perivascular lymphoeosinophilic inflammation	Dermal hypersensitivity reaction as a result of other bug/drug (lacks scabies mite)
Scar (cicatrix)	Horizontally arrayed ( <b>"East-West"</b> ) collagen and fibroblasts; vertical vessels +/- loss of rete ridges	DF (collagen trapping, epidermal hyperplasia), hypertrophic scar (whorled collagen and fibroblastic nodules), and Keloid (↓fibroblasts; keloidal collagen)
Schwannoma (neurilemmoma)	<b>Very deep (SQ or deeper)</b> nodular proliferation, peripheral capsule, large dilated/hyalinized vessels, <b>hypercellular Antoni A areas with Verocay bodies</b> , and hypocellular/myxoid <b>Antoni B</b> areas	NF (more superficial, haphazard proliferation rather than organized, lacks Antoni A and B areas, and lacks capsule), PEN (much more superficial (dermis), has nerve fascicles, and lacks Antoni A and B areas)
Scleredema	<b>Widely-spaced (but normal-sized) collagen bundles</b> with <b>markedly increased interstitial mucin</b> ; no increase in dermal spindle cells/fibroblasts	Normal back skin (lacks mucin), scleroderma/morphea (thickened/keloidal collagen, lacks mucin), scleromyxedema and NSF (increased spindle cells)
Scleroderma/morphea	<b>Square biopsy</b> sign, thickened collagen (sclerotic/keloidal/hyalinized), <b>loss of peri-adnexal fat</b> , PV inflammation w/ <b>plasma cells</b> , and <b>loss of CD34+ fibroblasts</b>	Scleredema (abundant interstitial mucin, normal-sized but widely spaced collagen bundles), Scleromyxedema and NSF (increased CD34+ spindled cells, mucin, less collagen thickening, and no loss of periadnexal fat), radiation dermatitis ("sick" or pale dermal collagen, dilated vessels)
Scleromyxedema (papular mucinosis)	Square biopsy sign, spindle cell proliferation w/ <b>↑interstitial mucin</b>	Scleroderma/morphea (lacks spindle cell proliferation and mucin), scleroderma (lacks spindle cell proliferation), NSF (similar, but extends deeper in SQ septae), pretibial myxedema (mucin more concentrated in mid dermis, widely spaced wispy collagen fibers, and less spindle cells)
Sclerosing lipogranuloma/paraffinoma	<b>"Swiss cheese"</b> -like clear holes in fat and dermis	None
Sebaceous adenoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Sebaceous carcinoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Seborrheic dermatitis	<b>Shoulder parakeratosis</b> , spongiotic dermatitis	Psoriasis (confluent parakeratosis, more epidermal hyperplasia, and less spongiosis), PRP (checkerboard parakeratosis + shoulder parakeratosis, follicular plugging)
SJS/TEN	<b>Confluent full-thickness epidermal necrosis</b> , <b>pauci-inflammatory</b> , +/- subepidermal bulla	EM (lacks confluent k'cyte necrosis, more inflammatory, and lacks eos), coma bulla (sweat gland necrosis), thermal burn/excoriation/acid burn (more uniform k'cyte necrosis rather than individual apoptotic cells), epidermal necrosis as a result of vessel occlusion/vasculitis (vessel damage is apparent, versus SJS/TEN where it must be absent)
Spiradenoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

Dx	Buzzwords/Essential Features	Most Tested DDX
Spitz nevus	<b>Symmetric, well-circumscribed</b> , begins and ends in nests, spindled and epithelioid melanocytes with enlarged <b>amphophilic or pink cytoplasm</b> , “raining down” pattern of nests and cells, <b>clefts</b> around junctional nests, epidermal hyperplasia, <b>Kamino bodies</b> (PAS+ pink BMZ material), maturation with depth, and central pagetoid scatter is acceptable	Melanoma (asymmetric, poorly circumscribed, often trails off as single junctional cells rather than nests, epidermal consumption/thinning, pagetoid scatter diffuse throughout lesion, increased mitotic rate, lacks maturation with depth), atypical Spitz nevus/tumor (somewhat subjective, but lacks some of the classically reassuring features of Spitz nevi; FISH or array CGH helpful in predicting aggressive lesions)
Sporotrichosis	<b>Cigar-shaped yeast</b> surrounded by granulomatous inflammation	None
Stasis dermatitis	Lobular proliferation of capillaries in superficial and mid dermis, RBC extravasation, hemosiderin, +/- epidermal spongiosis	Kaposi (interstitial and infiltrative proliferation rather than lobular, vessels are not well-formed capillaries), angiosarcoma (infiltrative architecture, hyperchromatic atypical cells w/ mitoses)
Steatocystoma	Collapsed empty cyst, <b>pink “shark-toothed” cuticle</b> , and sebaceous glands in wall	Epidermoid cyst (central keratin debris, lacks pink cuticle and sebaceous glands in wall); dermoid cyst (also has pink cuticle and sebaceous glands in wall; distinguished by presence of hair follicles in wall and central keratin debris)
Subcutaneous fat necrosis of newborn	<b>Radiating feathery crystals (“maple leaf-like”)</b> within lipocytes + dense <b>granulomatous inflammation</b>	Sclerema neonatorum (lacks granulomatous inflammation), gouty tophus (larger aggregates of needle-shaped crystals)
Subcutaneous panniculitis-like T-Cell lymphoma (SPTCL)	<b>Fat rimming</b> by atypical lymphocytes	Lupus profundus (nodular lymphoid aggregates w/ plasma cells, +/- mucin and interface changes), gamma-delta T-cell lymphoma (interface changes, beta-F1 negative)
Supernumerary digit	Polypoid, numerous well-formed nerve bundles	Acquired digital fibrokeratoma (lacks nerves), amputation neuroma (scar; nerve bundles not as well-formed)
Supernumerary nipple	Papillomatous epidermis, abundant smooth muscle, +/- lactiferous ducts	Acanthosis nigricans (lacks smooth muscle); Becker's nevus (lacks ducts)
Suture granuloma	Foreign body giant cells surrounding a cluster of <b>evenly sized, round or thread-like, polarizable suture</b> material	None
Sweet's syndrome	Diffuse <b>superficial to mid dermal neutrophilic infiltrate</b> w/ leukocytoclasia, marked <b>papillary dermal edema</b> ; lacks angiocentricity and primary vasculitis	LCV (angiocentric neutrophilic infiltrate w/ vascular damage, RBC extravasation; less dense infiltrate and does not have marked edema), PMLE (lymphocytic infiltrate w/ marked papillary dermal edema), Pyoderma gangrenosum (very similar to Sweet's but generally has less edema, deeper dermal/SQ neutrophilic infiltrate and ulceration with undermining neutrophilic inflammation)
Syphilis	<b>Psoriasiform hyperplasia</b> (with slender, <b>“sexy” long rete ridges</b> ), <b>lichenoid</b> interface, dirty infiltrate (neuts, <b>abundant plasma cells</b> ), and endothelial cell swelling	LP (lacks plasma cells), psoriasis (lacks interface and plasma cells)
Syringocystadenoma papilliferum	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Syringoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Talon noir	<b>Intracorneal</b> hemorrhage on acral site (foot #1)	None
Tattoo (lead)	Large pitch black clumps of dermal pigment	Blue nevus and dermal melanocytoses (melanin is not as dark in color), argyria (pigmented particles are much smaller and located preferentially around eccrine coils)
Tinea corporis	Hard to visualize <b>pale-staining hyphae</b> located within thin layer of compact eosinophilic stratum corneum immediately above granular layer ( <b>“holes in thickened pink corneum”</b> ), overlying basket weave orthokeratosis, <b>brisk dermal inflammation</b> , and occasional <b>subcorneal pustules</b>	Tinea versicolor (hyphae much easier to see on H&E; located more superficial in upper stratum corneum; minimal to no dermal inflammation; no pustules)
Tinea versicolor	<b>Easily visualized purple hyphae</b> in superficial stratum corneum, <b>minimal to no dermal inflammation</b>	Tinea corporis (hyphae in lower s.corneum, hyphae much harder to see, and vigorous dermal inflammation)
Traumatic/amputation neuroma	Multiple small nerve fascicles within scar	PEN (lacks scar; more circumscribed)
Trichilemmoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Trichilemmoma (desmoplastic variant)	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Trichoepithelioma	See Neoplastic Dermatology section	See Neoplastic Dermatology section

Continued

**Table 7-11.** Dermatopathology Diagnoses at a Glance—cont'd

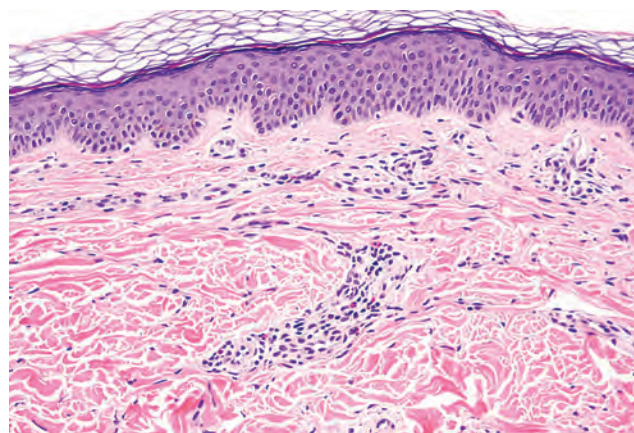
Dx	Buzzwords/Essential Features	Most Tested DDx
Trichoepithelioma (desmoplastic variant)	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Trichofolliculoma	See Neoplastic Dermatology section	See Neoplastic Dermatology section
Trichotillomania	<b>Trichomalacia</b> (distorted hair shafts), melanin <b>"pigment casts"</b> in follicle	Alopecia areata ("swarm of bees" pattern of peri-bulbar lymphocytic inflammation, eosinophils common around bulb, and fibrous streamer tracts containing lymphocytes, eos and pigment incontinence)
Vellus hair cyst	Large epidermoid cyst containing multiple vellus hairs	Steatocystoma (cysts are empty)
Verruca plana	Smooth acanthotic epidermis, mild hypergranulosis, and koilocytes superficially	EDV (blue-gray haze superficially)
Verruciform xanthoma	<b>Wart-like epidermal surface</b> with foamy/ <b>xanthomatized histiocytes stuffed in dermal papillae</b>	Wart and trichilemmoma (lack xanthoma cells)
Verrucous carcinoma	Looks like a huge wart with exo-endophytic architecture, <b>"pushing"</b> deep border, and minimal to no cytologic atypia	Condyloma acuminata (smaller, lacks deep "pushing" architecture), conventional SCC (more cytologic atypia, infiltrative rather than "pushing" deep border)
Warty dyskeratoma	<b>Endophytic ("cup-shaped")</b> , well-circumscribed, acantholytic dyskeratosis, corps ronds/grains	Darier's (less endophytic, less circumscribed), wart (lacks acantholytic dyskeratosis and corps ronds/grains), and acantholytic SCC (atypia + weird mitoses)
Well's syndrome (eosinophilic cellulitis)	<b>Flame figures</b> (eosinophil degranulation → deposits on collagen) w/ numerous eosinophils	None
Xanthelasma	Eyelid skin + foamy histiocytes	Eruptive xanthoma (noneyelid skin, extracellular lipid), JXG (Touton giant cells, granulomatous infiltrate, and eosinophils)
Zoon's balanitis (plasmacytosis mucosae)	Flattened k'cytes, band-like <b>plasma cell infiltrate</b> , and RBC extravasation	LP (more apoptotic k'cytes, predominantly lymphocytes with only scattered plasma cells), plasmacytoma (atypical or binucleate plasma cells, mitoses, Dutcher bodies)
Zygomycosis	Broad, nonseptated, <b>pink</b> hollow hyphae with 90° branching, <b>angioinvasive fungal elements</b> , <b>thrombotic vessels</b> with subsequent epidermal/dermal necrosis	Hyalohyphomycosis (narrow, septated, blue hyphae with bubbly cytoplasm, 45° branching; angioinvasive with subsequent epidermal/dermal necrosis)

### 7.3 HIGH-YIELD DERMATOPATHOLOGY DIFFERENTIAL DIAGNOSES

Text continued on p. 409

**Table 7-12.** "Normal Skin" DDx

<b>Macular amyloid</b>	<b>Light pink</b> deposits papillary dermis; pigment incontinence/melanophages
<b>TMEP</b>	Superficial dermal <b>telangiectasias</b> + sparse proliferation of <b>spindled mast cells</b> ; may need <b>CD117</b> immunostain or other mast cell stain (Leder, Tryptase, or Giemsa) to confirm (Fig. 7-13)
<b>Tinea corporis</b>	<b>Pale-staining hyphae</b> in lower stratum corneum, <b>brisk dermal inflammation</b> , +/- subcorneal pustule
<b>Tinea versicolor</b>	<b>Basaloid spores and hyphae</b> ("spaghetti and meatballs") in <b>upper stratum corneum</b> , much easier to see than tinea corporis, and <b>minimal to no dermal inflammation</b>
<b>Argyria</b>	Small black granules in <b>sweat glands</b>
<b>Ichthyosis vulgaris</b>	<b>Compact orthohyperkeratosis</b> w/ paradoxically ↓ <b>granular layer</b> (almost all other diseases w/ orthohyperkeratosis have ↑granular layer)
<b>Erythrasma</b>	Organisms one fifth the size of hyphae; vertical filaments in stratum corneum



**Figure 7-13.** Telangiectasia macularis eruptiva perstans. There is a light perivascular infiltrate. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier. 2011)

#### Box 7-1. Mnemonic

"Busy dermis DDx = **B**usy **D**ermis **C**an **K**ill **G**randma's **S**weet **N**iece **L**ucy"

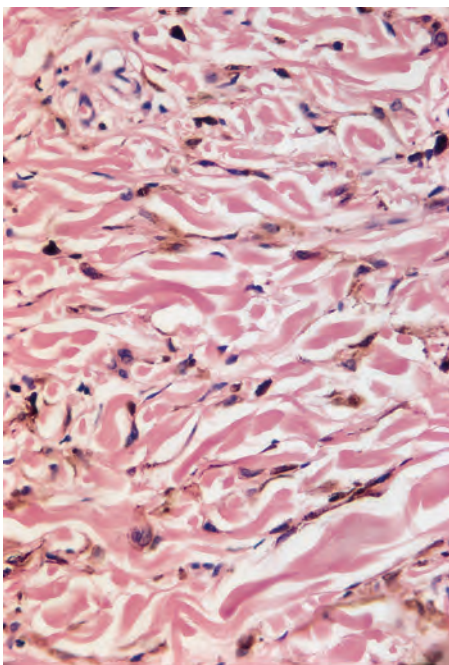
**B**lue nevus, **D**ermatofibroma/Dermal spitz, **C**utaneous metastasis, **K**aposi's (plaque), **G**ranuloma annulare, **S**cleromyxedema, **N**eurofibroma, **L**eukemia cutis

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

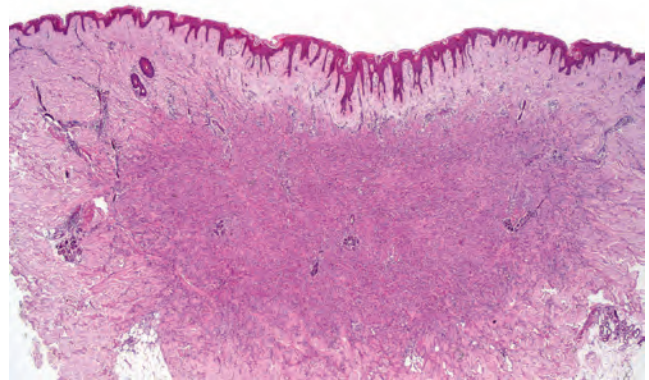


**Table 7-13.** Busy Dermis Ddx

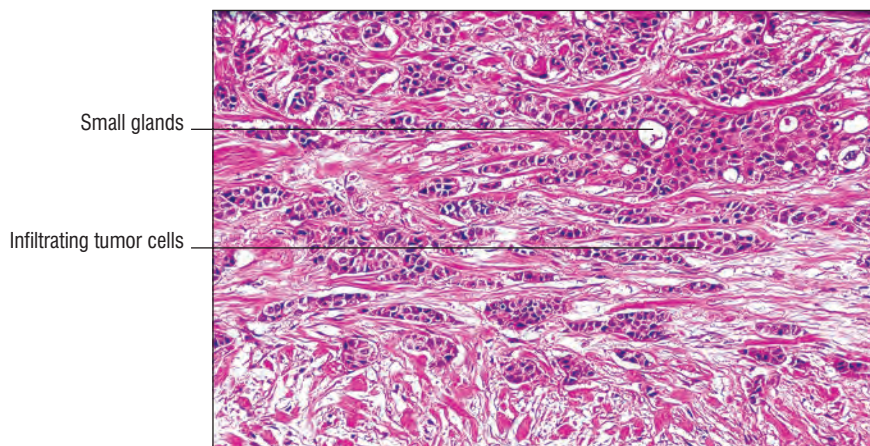
<b>Blue nevus</b>	Paucicellular <b>dendritic melanocyte</b> proliferation within <b>sclerotic stroma</b> , melanophages, and HMB-45 diffusely positive (vs stratified staining in conventional nevi) (Fig. 7-14)
<b>Dermatofibroma</b>	Interstitial spindle cell proliferation, <b>collagen trapping</b> , epidermal/follicular <b>induction</b> , <b>curlicue pattern</b> , hemosiderin-laden histiocytes/Touton-like GCs, <b>factor XIIIa<sup>+</sup></b> , and <b>CD34<sup>+</sup></b> (Fig. 7-15)
<b>Cutaneous metastasis</b>	Most commonly tested: metastatic <b>breast CA</b> (“ <b>Indian-filing</b> ,” <b>small ducts</b> ), <b>RCC</b> ( <b>clear cells</b> , <b>highly vascular</b> ), colon CA (“dirty necrosis”); although not always true, a rule of thumb to help determine primary tumor location is: <b>CK7<sup>+</sup></b> (above diaphragm), versus <b>CK20<sup>+</sup></b> (below diaphragm) (Figs. 7-16, 7-17, and 7-18)
<b>Kaposi sarcoma (plaque)</b>	Relatively <b>bland interstitial spindle cell proliferation</b> , “ <b>promontory sign</b> ,” vascular wrapping, thin <b>slit-like vascular spaces</b> , extravasated RBCs, and increased <b>plasma cells</b> (most easily seen in perivascular distribution near tumor) (Fig. 7-19); <b>HHV-8<sup>+</sup></b>
<b>GA (interstitial)</b>	Interstitial histiocytes w/ foci of altered collagen, <b>↑mucin</b> (Fig. 7-20)
<b>Scleromyxedema</b>	Bland dermal spindled fibroblastic proliferation w/ fine <b>collagen fibers</b> ; <b>↑mucin</b> (Fig. 7-21)
<b>Neurofibroma</b>	Loosely arranged spindle cells with <b>wavy/ “buckled” nuclei</b> , <b>myxoid stroma</b> , and <b>↑mast cells</b> (Fig. 7-22)
<b>Leukemia cutis</b>	Interstitial infiltrate of atypical cells w/ “ <b>blast</b> ” morphology (fine chromatin, prominent nucleoli, and larger than normal inflammatory cells) arranged in “ <b>Indian-file</b> ” pattern; <b>frequent mitoses</b> ; myeloid/monocytic leukemias typically positive for <b>CD68</b> and <b>lysozyme</b> (two most sensitive markers) > <b>MPO</b> > <b>CD34</b> and <b>CD117</b> (Fig. 7-23)



**Figure 7-14.** Blue nevus. Melanocytes with long dendritic processes and cytoplasmic melanin are present between the collagen bundles of the dermis. (From Weedon D. *Weedon's Skin Pathology*, 3rd ed. Elsevier. 2009)



**Figure 7-15.** Dermatofibroma: scanning section showing the characteristic architecture. The lateral borders of the lesion interdigitate with the adjacent dermis. There is hyperkeratosis and acanthosis of the overlying epidermis. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)



**Figure 7-16.** Metastatic breast carcinoma. (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)



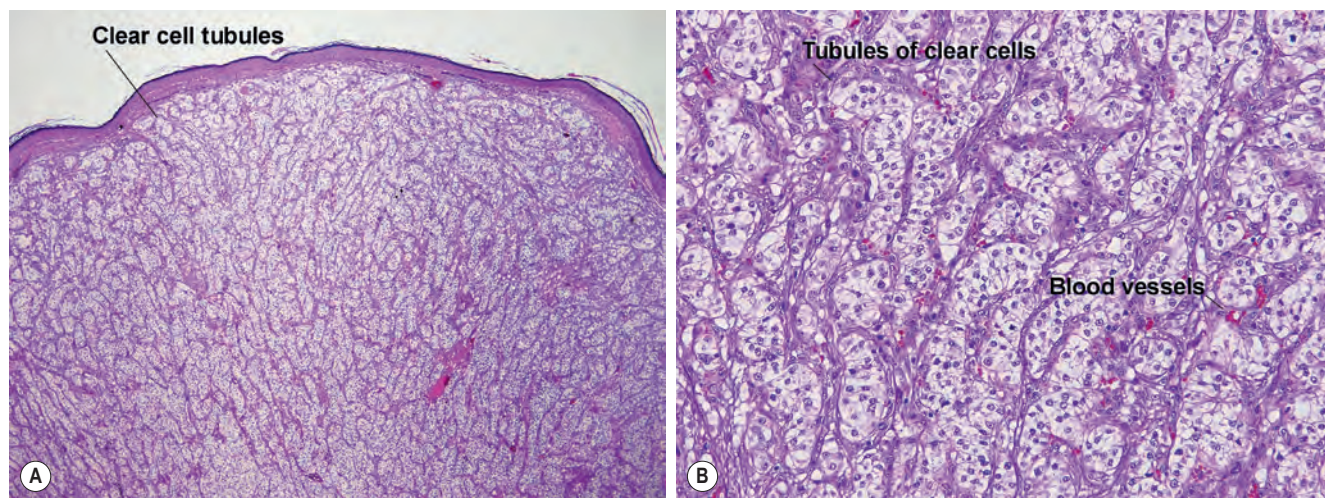


Figure 7-17. Renal carcinoma. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

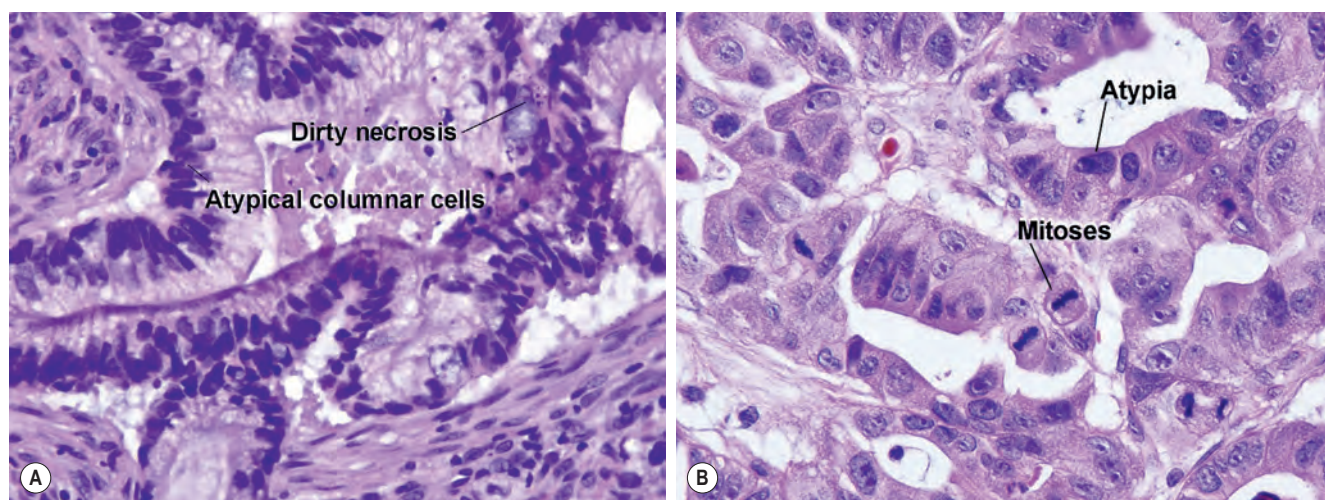


Figure 7-18. (A, B) Colon carcinoma. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

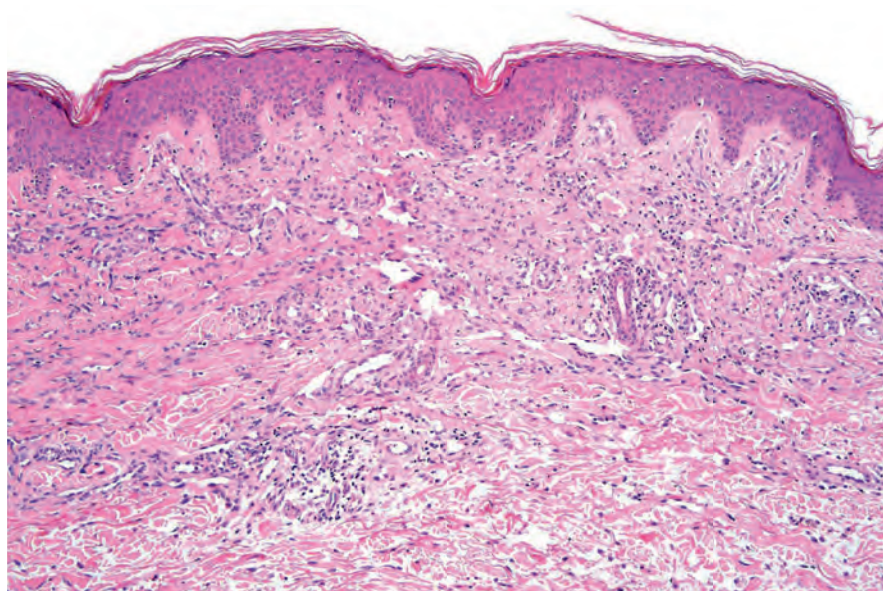
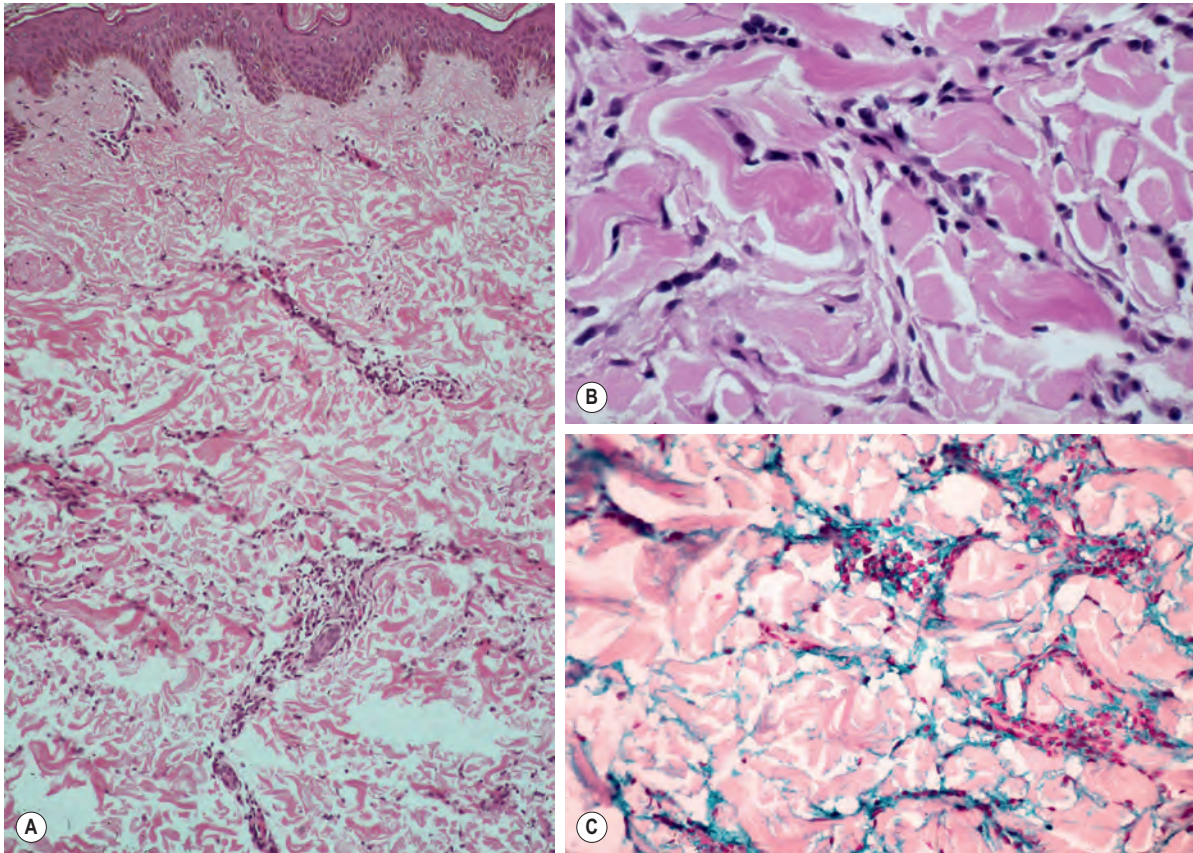
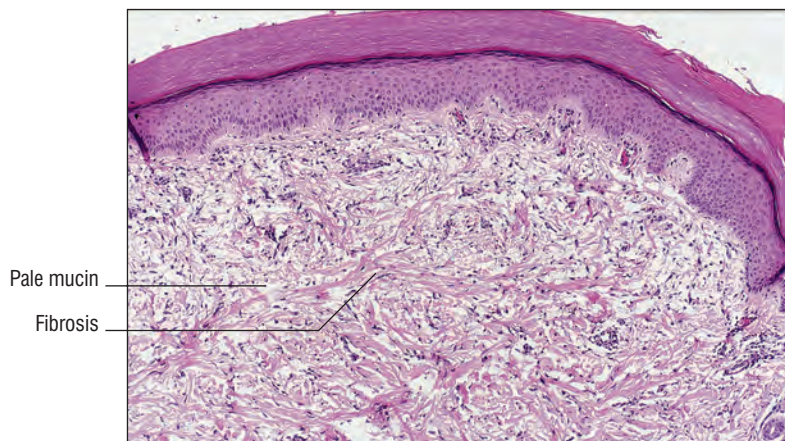


Figure 7-19. Kaposi sarcoma (patch stage): there is increased vascularity, spindle cells, and a light chronic inflammatory cell infiltrate. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011 <https://expertconsult.inkling.com/store/book/elston-dermatopathology-2nd/https://expertconsult.inkling.com/store/book/mckees-pathology-of-the-skin-calonne-brenn-lazar-mckee-4th/>)

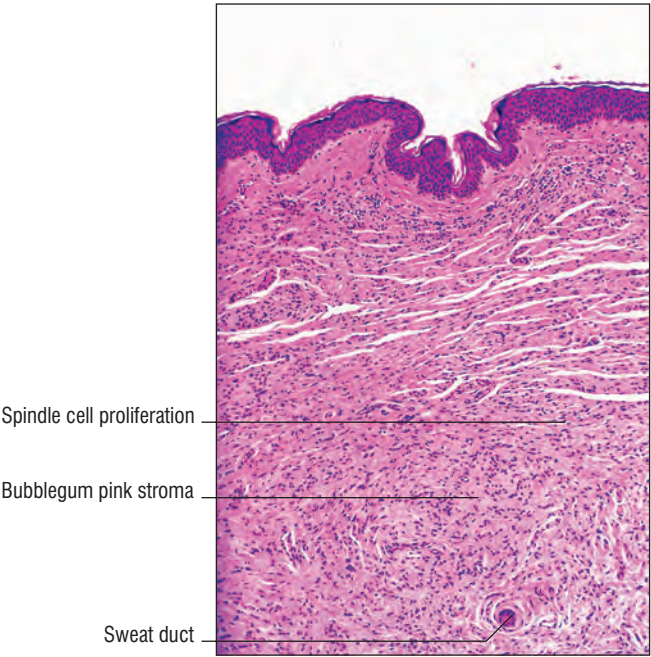




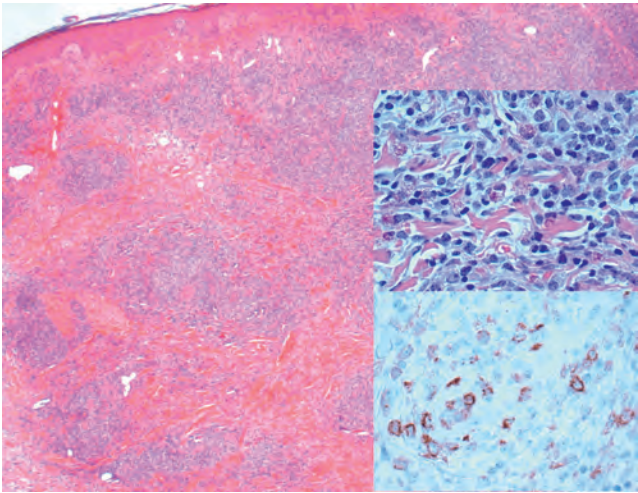
**Figure 7-20.** (A) Granuloma annulare of 'incomplete' type. (B) The dermis is hypercellular (a so-called 'busy dermis') (H&E). (C) There is an increased amount of interstitial mucin (Alcian blue). (From Weedon D. *Weedon's Skin Pathology*, 3rd ed. Elsevier. 2009)



**Figure 7-21.** Scleromyxedema. (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)



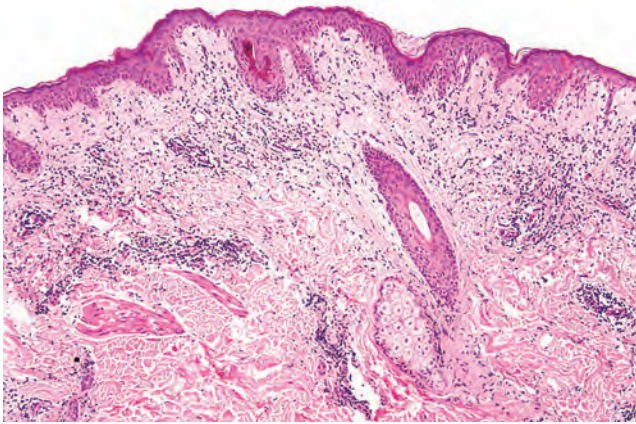
**Figure 7-22.** Neurofibroma. (From Rapini R. Practical Dermatopathology, 2nd Ed. Elsevier. 2012)



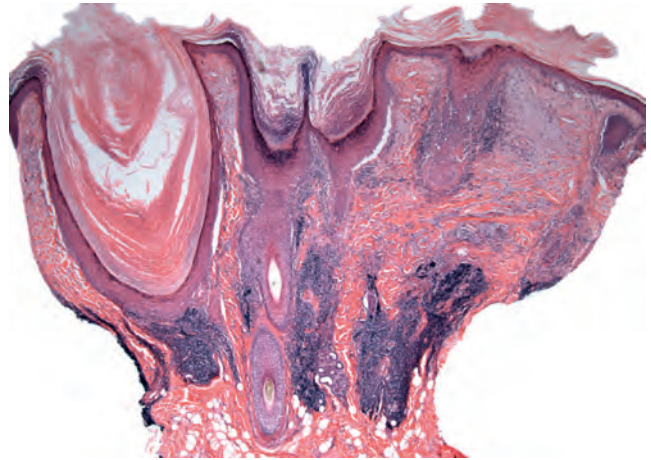
**Figure 7-23.** Acute myeloid leukemia. There is a heavy infiltrate of blasts, some of which contain conspicuous eosinophilic granules (top inset). Some cells are positive for myeloperoxidase. (From Weedon D. Weedon's Skin Pathology, 3rd ed. Elsevier. 2009)

Table 7-14. Vacuolar Interface Dermatitis DDx	
<b>Lupus erythematosus (SCLE)</b>	Orthohyperkeratosis; <b>brisk vacuolar interface</b> diffusely affecting epidermis, <b>superficial (&gt; deep) PV/PA lymphocytic infiltrate</b> , BMZ thickening, ↑mucin; lacks eosinophils (Fig. 7-24)
<b>Lupus erythematosus (Discoid)</b>	Orthohyperkeratosis; <b>moderate vacuolar interface centered around follicular epithelium</b> (> interfollicular epidermis), <b>hyperplastic follicular infundibulae</b> (esp. hypertrophic DLE), dilated follicles w/ <b>follicular plugging</b> , interfollicular epidermal atrophy, <b>dermal fibrosis/scar</b> , <b>superficial and deep PV/PA lymphocytic infiltrate</b> , BMZ thickening, and ↑mucin; lacks eosinophils (Fig. 7-25)
<b>Dermatomyositis</b>	Orthohyperkeratosis, epidermal atrophy, sparse lymphocytic infiltrate (< LE), <b>minimal vacuolar interface</b> (< LE, EM, FDE, and PLEVA), and <b>↑↑↑dermal mucin</b> (> LE); telangiectasias; <b>lacks deep PV/PA inflammation</b> (vs LE), lacks eosinophils (Fig. 7-26)
<b>Erythema multiforme</b>	<b>Basket-weave</b> (acute) stratum comeum, prominent apoptotic keratinocytes scattered throughout <b>all levels</b> of epidermis, superficial lymphocytic infiltrate w/ lymphocyte exocytosis; lacks eosinophils (vs frequent eosinophils in SJS/TEN and FDE) (Fig. 7-27)
<b>Fixed drug eruption</b>	<b>Basket-weave</b> (acute) stratum corneum, <b>EM-like vacuolar interface</b> , <b>chronic dermal changes</b> (deeper <b>pigment incontinence</b> , papillary dermal fibrosis), and mixed dermal inflammation w/ numerous <b>eosinophils</b> (Fig. 7-28)
<b>Acute GVHD</b>	<b>Orthohyperkeratosis</b> , EM-like vacuolar interface, <b>k'cyte dysmaturation</b> (from <b>chemo effect</b> ), " <b>satellite cell necrosis</b> "; frequently involves follicular epithelium (Fig. 7-28)
<b>PLEVA</b>	<b>P</b> arakeratosis, <b>L</b> ichenoid-to-vacuolar interface, <b>E</b> rythrocyte extravasation, <b>V</b> -shaped (wedge) lymphocytic infiltrate, <b>A</b> cute surface changes (scale crust +/- ulceration); <b>never has eosinophils</b> (if more than a few eosinophils present → not PLEVA!) (Fig. 7-29)

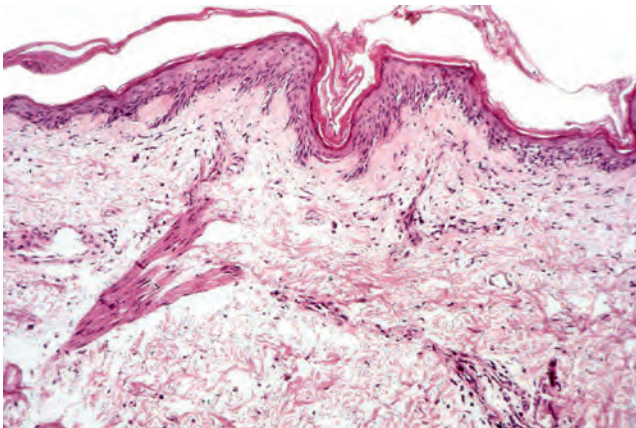




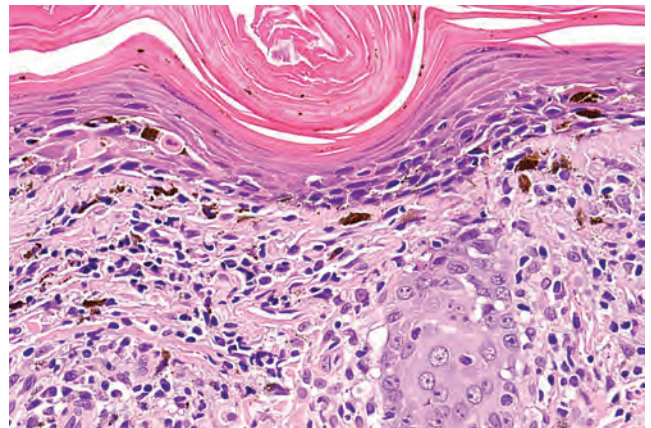
**Figure 7-24.** Subacute cutaneous lupus erythematosus. At low power, the features are subtle. There is slight hyperkeratosis and a perivascular chronic inflammatory cell infiltrate is present. (Courtesy of E Calonje, MD; St John's Dermatology Center, London.) (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier. 2011)



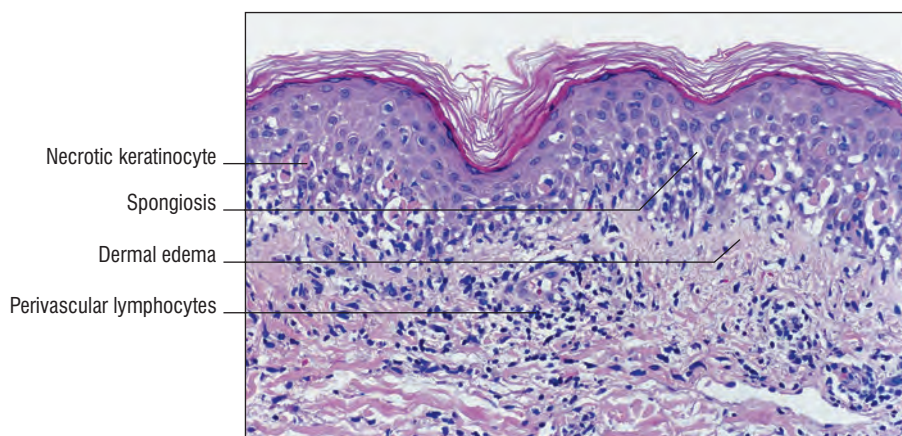
**Figure 7-25.** Discoid lupus exhibits follicular plugging, superficial and deep perivascular and perifollicular lymphocytes. There is interfollicular atrophy and interface dermatitis affecting both the epidermis and follicular epithelium. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd edn. Elsevier, 2015)



**Figure 7-26.** Dermatomyositis: there is hyperkeratosis, epidermal atrophy, mild basal vacuolar change and marked increase in dermal mucin. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)

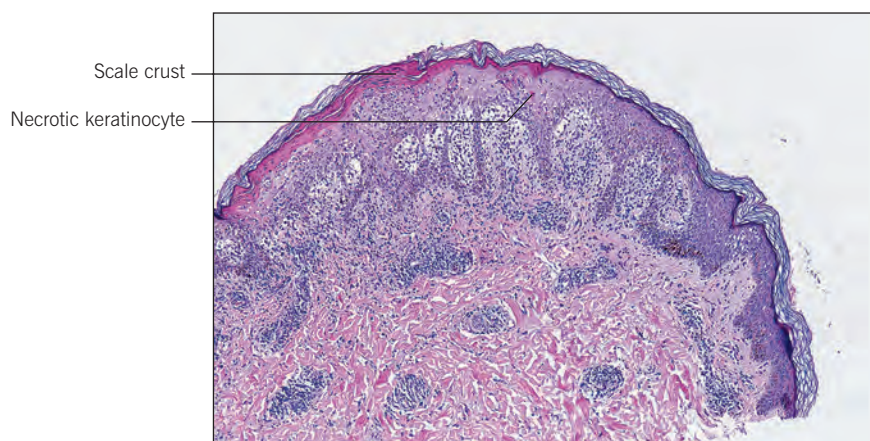


**Figure 7-28.** Acute graft-versus-host disease. There is hyperkeratosis, epidermal atrophy, cytoid bodies, and interface change. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier. 2011)



**Figure 7-27.** Erythema multiforme. (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)





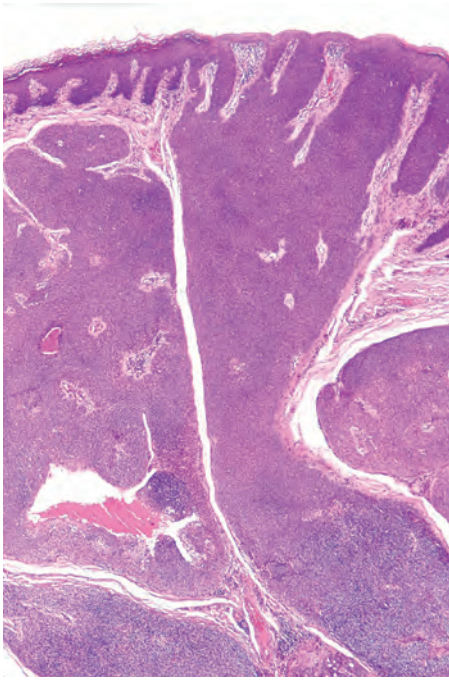
**Figure 7-29.** Pityriasis lichenoides (low mag). (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)

**Table 7-15.** Lichenoid Interface Dermatitis DDX

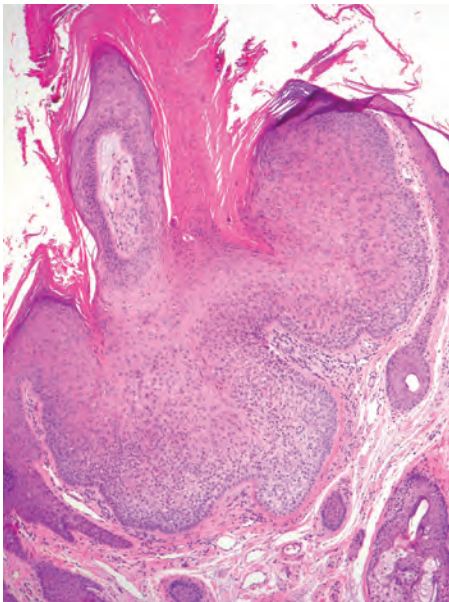
<b>Lichen Planus</b>	Orthohyperkeratosis, <b>irregular acanthosis</b> , <b>V-shaped hypergranulosis</b> , <b>“saw-toothed” rete ridges</b> , and <b>apoptotic keratinocytes limited to lower levels of epidermis</b> ; lacks eosinophils (exceptions = hypertrophic LP, drug-induced LP), lacks deep PV/PA inflammation
<b>Lichen Planus-Like Keratosis (BLK)</b>	Like LP, but may have <b>parakeratosis</b> , <b>eosinophils</b> ; frequently see solar lentigo/SK at periphery
<b>Lichenoid Drug Eruption</b>	Looks like LP, but often has <b>parakeratosis</b> and deeper PV inflammatory infiltrate <b>w/ eosinophils</b>
<b>Lichenoid GVHD</b>	Infiltrate less dense than LP, <b>satellite cell necrosis</b> , and epidermis often has <b>chemotherapy effect/dysmaturation</b>
<b>Melanoma w/ Lichenoid Regression</b>	Search periphery for atypical melanocytic lesion; prominent pigment incontinence at regressed area
<b>Lichen Nitidus</b>	Small circumscribed papule, <b>“ball and claw,”</b> and <b>epidermal collarette</b> ; dermal infiltrate is more mixed, consisting of lymphocytes, histiocytes, and giant cells
<b>Lichen Striatus</b>	Similar to LP, but w/ <b>↑spongiosis</b> and <b>deep peri-ecrine inflammation</b>
<b>Lichenoid Pigmented Purpura</b>	Lichenoid and PV lymphocytic inflammation w/ <b>RBC extravasation and hemosiderin</b> deposition
<b>Lichenoid Secondary Syphilis</b>	<b>“Dirty” infiltrate</b> (lymphocytes, <b>neutrophils</b> , histiocytes, nuclear debris, and <b>plasma cells</b> ), <b>slender elongated rete</b>
<b>Hypertrophic Lupus Erythematosus</b>	<b>Mistaken for SCC</b> because of the hyperplastic follicular epithelium (unlike SCC, the <b>interfollicular epidermis is typically normal-atrophic</b> ); lichenoid infiltrate resembles LP but has other features of lupus: <b>deep PV/PA inflammation</b> , <b>↑mucin</b> , and BMZ thickening

**Table 7-16.** Weird Endophytic Neoplasms DDX

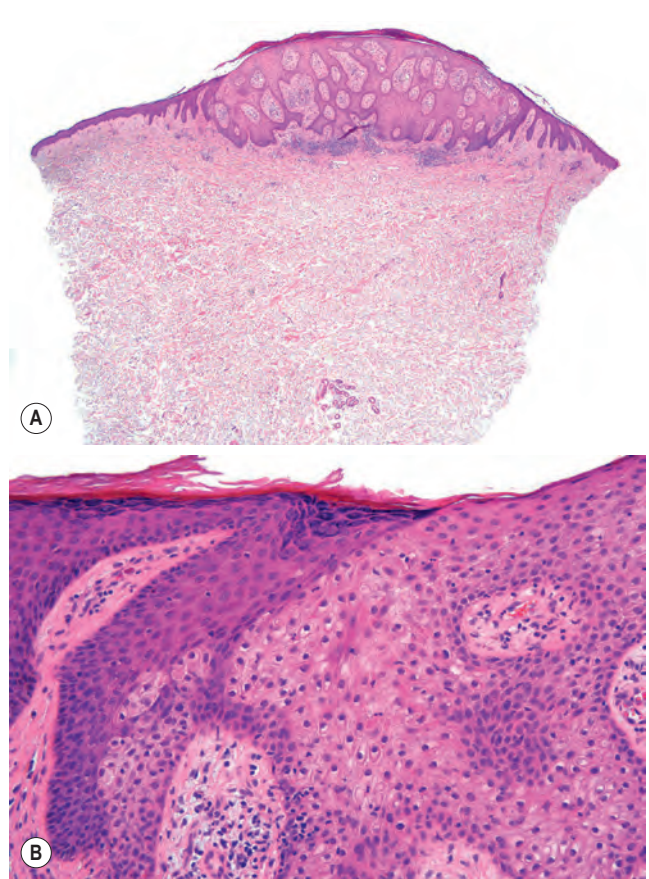
<b>Ecrrine Poroma</b>	Uniform small cuboidal (“poroid”) cells; multi-focal epidermal connections; <b>eosinophilic cuticle in ducts</b> (Fig. 7-30)
<b>Trichilemmoma</b>	Lobular architecture, <b>clear (glycogenated) cells w/ peripheral palisade</b> and thick <b>eosinophilic BMZ</b> , +/- squamous eddies, +/- verrucous surface (Fig. 7-31)
<b>Clear Cell Acanthoma</b>	<b>Psoriasiform</b> hyperplasia w/ <b>neutrophils</b> in corneum, <b>sharply demarcated</b> from surrounding normal epidermis (“looks exactly like psoriasis but with clear cells”) (Fig. 7-32)
<b>Pilar Sheath Acanthoma</b>	Acanthotic lobules attached to dilated pore (“dilated pore of Winer on steroids”) (Fig. 7-33)
<b>Tumor of Follicular Infundibulum</b>	Multiple slender connections to epidermis; fenestrated <b>“plate-like” architecture</b> (Fig. 7-34)
<b>Trichoepithelioma</b>	Basaloid tumor cells within <b>highly cellular pink (fibroblast-rich) dermis</b> ; minimal to no epidermal attachment (vs vast majority of BCCs); <b>papillary mesenchymal bodies</b> and <b>numerous horn cysts</b> (many calcified) (Fig. 7-35)
<b>Ecrrine Syringofibroadenoma</b>	Multiple epidermal connections; anastomosing strands of epithelial cells, <b>ducts</b> , and fibrovascular stoma (Fig. 7-36)



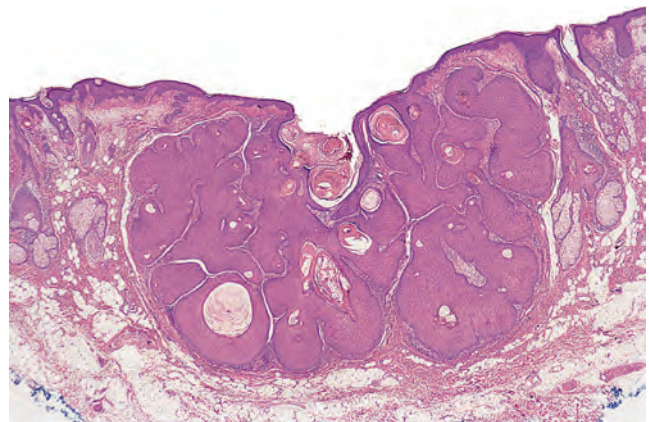
**Figure 7-30.** Eccrine poroma: this scanning view shows interconnected epithelial down-growth with multiple foci of attachment to the epidermis. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)



**Figure 7-31.** Trichilemmoma. An exophytic verrucous growth pattern is associated with a lobular perifollicular clear cell proliferation at the base of the lesion. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2e. Elsevier. 2015)



**Figure 7-32.** Clear cell acanthoma: (A) the lesion, which is sharply demarcated, shows striking hyperplasia; (B) although the basal epithelial cells retain their normal tinctorial properties, most of the epithelium shows marked pallor. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)



**Figure 7-33.** Pilar sheath acanthoma. Tumor lobules, composed of outer root sheath epithelium, radiate from a central depression. (From Weedon D. *Weedon's Skin Pathology*, 3rd ed. Elsevier. 2009)



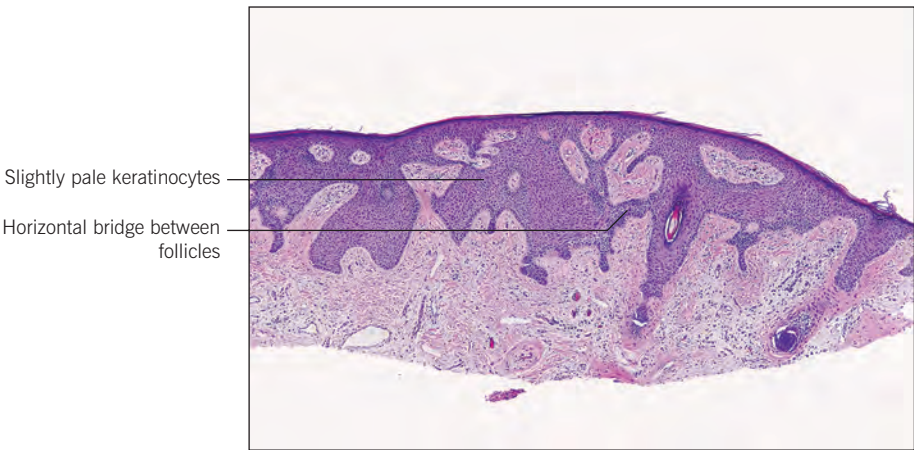


Figure 7-34. Tumor of follicular infundibulum. (From Rapini R. Practical Dermatopathology, 2nd Ed. Elsevier.2012)

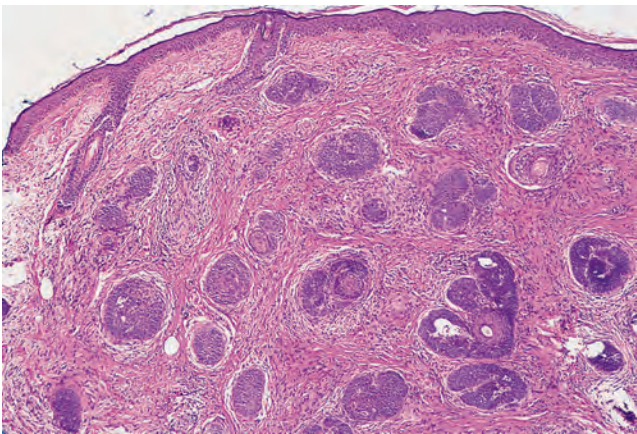


Figure 7-35. Trichoepithelioma. There are multiple nests of basaloid cells, some showing abortive hair follicle differentiation. (From Weedon D. Weedon's Skin Pathology, 3rd ed. Elsevier. 2009)

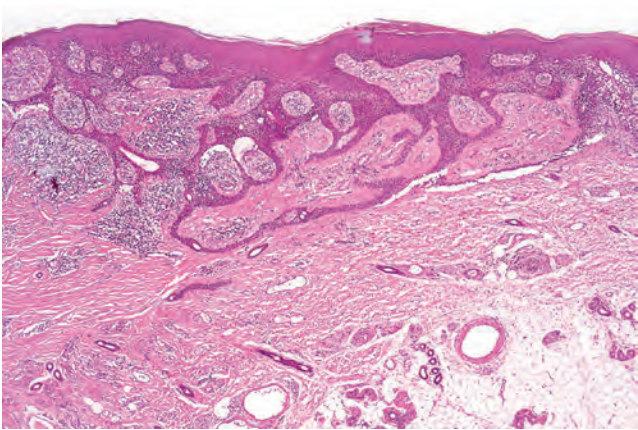


Figure 7-36. Eccrine syringofibroadenoma: this lesion presented as a solitary tumor. Arising from the epidermis are numerous anastomosing strands of epithelium surrounded by a cellular fibrous stroma. (From Calonje E, et al. McKee's Pathology of the Skin, 4th Ed. Elsevier. 2011)

Table 7-17. Paisley Tie ("Tadpole") DDx	
<b>Desmoplastic Trichoepithelioma</b>	<b>Central dell</b> , bland basaloid epithelial strands, <b>numerous horn cysts</b> (many w/ <b>calcification</b> ), and <b>fibroblast-rich pink collagenous stroma</b> ; lacks: retraction, myxoid stroma, and perineural involvement (Fig. 7-37)
<b>Microcystic Adnexal Carcinoma</b>	<b>Deeply infiltrative tumor</b> (into subcutis/ skeletal muscle almost always) with <b>bi-lineage</b> differentiation: horn cysts ( <b>follicular</b> ) and small syringoma-like ducts ( <b>sweat</b> ) in superficial dermis + infiltrative epithelial strands in deep dermis/SQ/ skeletal muscle; <b>perineural invasion</b> ; scattered <b>lymphoid nodules</b> (Fig. 7-38)
<b>Morpheaform Basal Cell Carcinoma</b>	<b>Sharply angulated</b> strands of atypical basaloid cells in morphea-like stroma, deeply invasive, numerous <b>mitoses</b> and <b>apoptotic cells</b> ; fewer horn cysts and calcifications than DTE; lacks ductal differentiation (vs MAC and syringoma) and lymphoid nodules (vs MAC) (Fig. 7-39)
<b>Syringoma</b>	Basaloid epithelial strands and <b>ducts</b> in fibrotic stroma; ducts contain amorphous eosinophilic debris; <b>lacks follicular differentiation</b> (vs MAC, DTE and BCC) (Fig. 7-40)

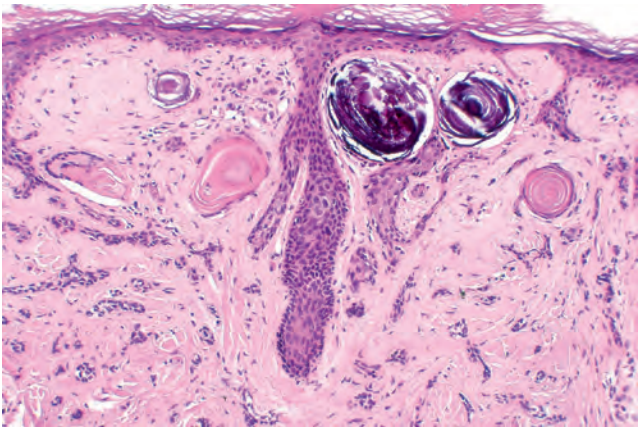
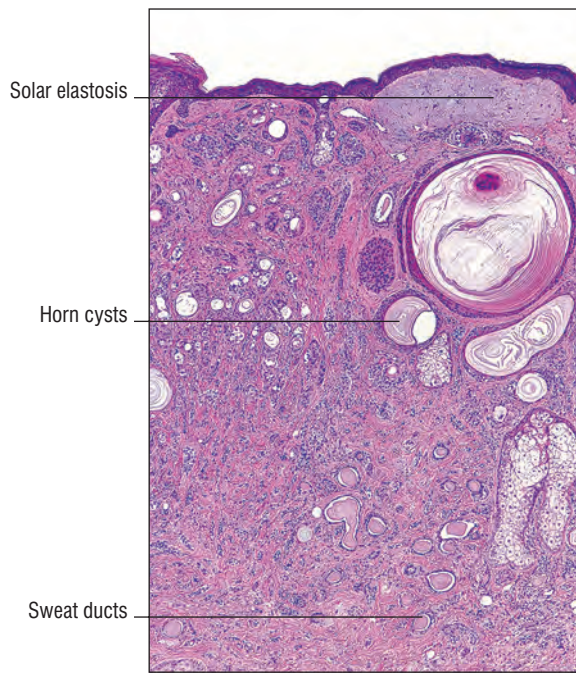
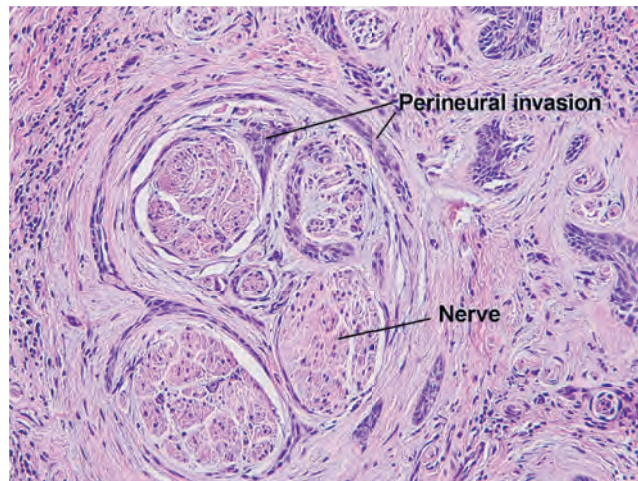


Figure 7-37. Desmoplastic trichoepithelioma: focal calcification as shown in this field is a very common feature. (From Calonje E, et al. McKee's Pathology of the Skin, 4th Ed. Elsevier. 2011)





**Figure 7-38.** Microcystic adnexal carcinoma. (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)



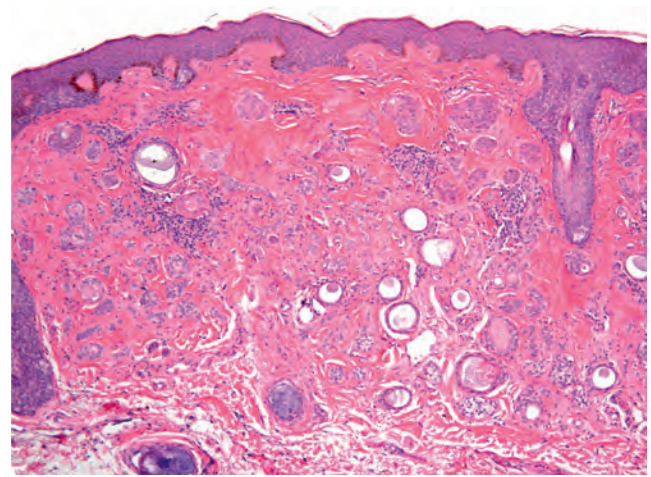
**Figure 7-39.** Morpheaform basal cell carcinoma. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

**Table 7-18.** Complex Cystic Proliferations ("Rolls and Scrolls")

<b>Proliferating Pilar cyst</b>	Dense pink trichilemmal keratin within cyst cavities; lacks granular layer; multilobular proliferations of squamous epithelium; lacks anucleate ghost cells
<b>Pilomatricoma</b>	Multilobulated dermal tumor; basaloid and ghost cells within the tumor lobules; calcification typically present +/- ossification

**Table 7-19.** Epidermoid Cyst Mimickers

<b>Vellus hair cyst</b>	Small <b>vellus hairs</b> within cyst cavity
<b>Dermoid cyst</b>	Complete array of <b>adnexal structures</b> (follicles, sebaceous glands, and apocrine glands) in cyst wall
<b>Steatocystoma</b>	Sebaceous glands in cyst wall, <b>eosinophilic cuticle</b> ("sharktooth" lining), and cyst cavity appears empty and collapsed



**Figure 7-40.** Syringoma. (From Weedon D. *Weedon's Skin Pathology*, 3rd ed. Elsevier. 2009)

**Table 7-20.** "Blue Balls in Dermis"

<b>Cylindroma</b>	Multiple basaloid tumor micronodules fused together in <b>jigsaw pattern</b> , small ducts, and thick <b>hyaline (pink) BMZ material surrounds</b> each tumor micronodule
<b>Spiradenoma</b>	Larger basophilic dermal nodules w/ <b>sweat ducts</b> , <b>hyaline droplets within</b> tumor micronodules, and <b>lymphocytes "peppered into tumor"</b>
<b>Dermal duct tumor</b>	Nodule of <b>monomorphous poroid cells</b> w/ cuticle-lined sweat ducts
<b>Glomus tumor</b>	Monomorphous <b>glomus cells encircling delicate blood vessels</b> ; lacks sweat ducts (vs dermal duct tumor)
<b>Hidradenoma</b>	Nodule comprised of a mixture of <b>squamoid and clear cells</b> w/ <b>sweat ducts</b> ; <b>keloidal/hyalinized stroma</b> ; +/- cystic degeneration ("solid-cystic hidradenoma")
<b>Trichoblastoma</b>	Dermal/SQ basaloid nodules (solid or cribiform), <b>fibroblast-rich pink collagenous stroma</b> , <b>papillary mesenchymal bodies</b> , and horn cysts; lacks stromal mucin and retraction (vs BCC), lacks ducts (vs sweat gland neoplasms)

**Table 7-21.** Clonal SK vs. Hydroacanthoma Simplex vs. Bowen's Disease

<b>Clonal SK</b>	Intraepidermal nests of k'cytes w/ minimal atypia; cell size $\geq$ surrounding k'cytes; lacks ducts
<b>Hydroacanthoma simplex</b>	Acanthotic epidermis w/ intraepidermal nests of <b>small poroid cells</b> (smaller than surrounding keratinocytes); <b>small ducts</b> present at least focally
<b>Bowen's disease</b>	Full thickness keratinocyte atypia (" <b>windblown</b> " appearance) w/ <b>atypical mitoses</b> , <b>dyskeratotic keratinocytes</b> (not seen in other two entities)



Table 7-22. Pagetoid DDX		
Disease	Essential Features	Immunostaining Profile
Pagetoid Bowen's disease	Clear cytoplasm, intercellular bridges, and involves basal layer	CK5/6+, CK7– (usually), BerEP4– (always)
EMPD/Paget's disease	<b>Mucin</b> in cytoplasm; nests of Paget cells compress the healthy basal layer of keratinocytes; +/- ducts	<b>Cytokeratin 7+</b> , <b>CK20–</b> , CEA+, BerEP4+ (helps to distinguish from Pagetoid Bowen's, which is always negative)
Melanoma in situ	Pigmented, expect to see some nesting at base of rete	S100+, Melan-A+, HMB-45+
Mycosis Fungoides	<b>Lymphocytes lining up at DEJ</b> ; irregular nuclear contours (" <b>cerebriform</b> "), <b>perinuclear halo</b> around lymphocytes ("lumps of coal resting on a pillow"), and " <b>wiry</b> " <b>papillary dermal fibrosis</b> (abnormally thickened collagen fibers in papillary dermis entrapping lymphocytes)	CD3+, CD4+, CD8– Often has loss of CD5 and CD7

Table 7-23. Square Biopsy DDX		
Disease	Increased Cellularity?	Essential Features
Chronic radiation dermatitis	No	Homogenized (" <b>sick-appearing</b> ") <b>dermis</b> , prominent superficial telangiectasias, <b>stellate fibroblasts</b> (Fig. 7-41), and <b>loss of adnexae</b>
NLD	<b>Yes (granulomatous)</b>	Diffuse granulomatous inflammation w/ " <b>cake-layered</b> " <b>necrobiosis</b> , dermal sclerosis (late-stage), <b>multinucleated GCs</b> , and <b>↑plasma cells</b>
Normal skin of the back	No	Normal thickness of collagen bundles – they just extend deeper!
Scar	<b>Yes (fibroblasts)</b>	" <b>East-West</b> " <b>collagen orientation</b> w/ ↑fibroblast cellularity, vertically oriented blood vessels Hypertrophic scars have "whorled" fibroblastic nodules
SclerEdema	No	↑ <b>space</b> and ↑ <b>mucin</b> between normal-sized collagen fibers (Fig. 7-42)
SclerOderma/ Morphea	No (exception: early/inflammatory morphea has perivascular lymphoplasmacytic inflammation)	<b>Thick hyalinized (pink) collagen bundles</b> , loss of perieccrine fat, and deep PV inflammatory infiltrate with <b>plasma cells</b> (Fig. 7-43)
Sclerodermoid GVHD	No	Thick collagen bundles, <b>mild vacuolar interface</b> , pigment incontinence, and loss of adnexae
Scleromyxedema/ NSF	<b>Yes (fibroblasts)</b>	↑ <b>fibroblasts</b> in dermis (NSF extends deeper into SQ), mild collagen thickening, and ↑ <b>mucin</b> (Fig. 7-44)

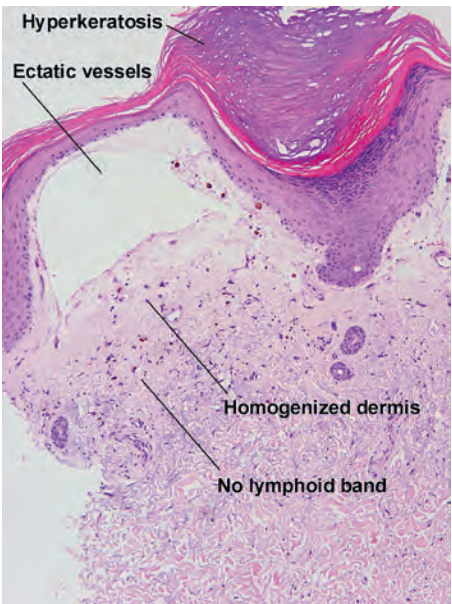


Figure 7-41. Chronic radiation dermatitis. (From Elston D, et al. Dermatopathology, 2nd Ed. Elsevier. 2013)

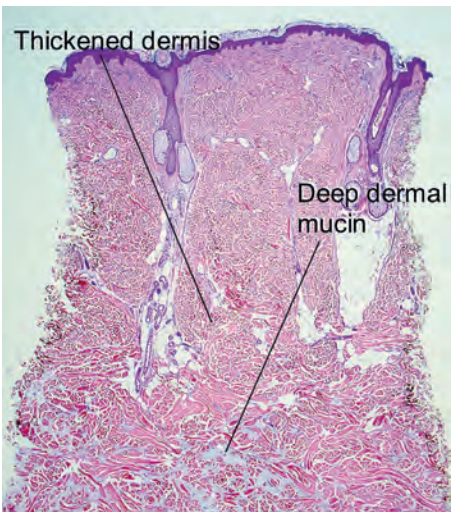
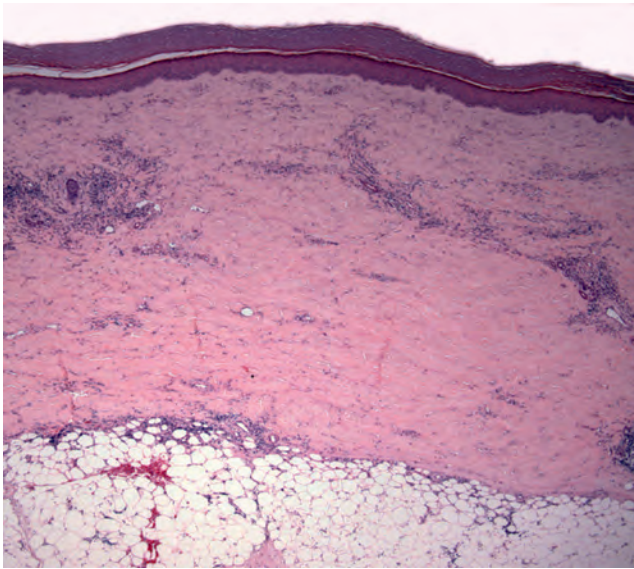


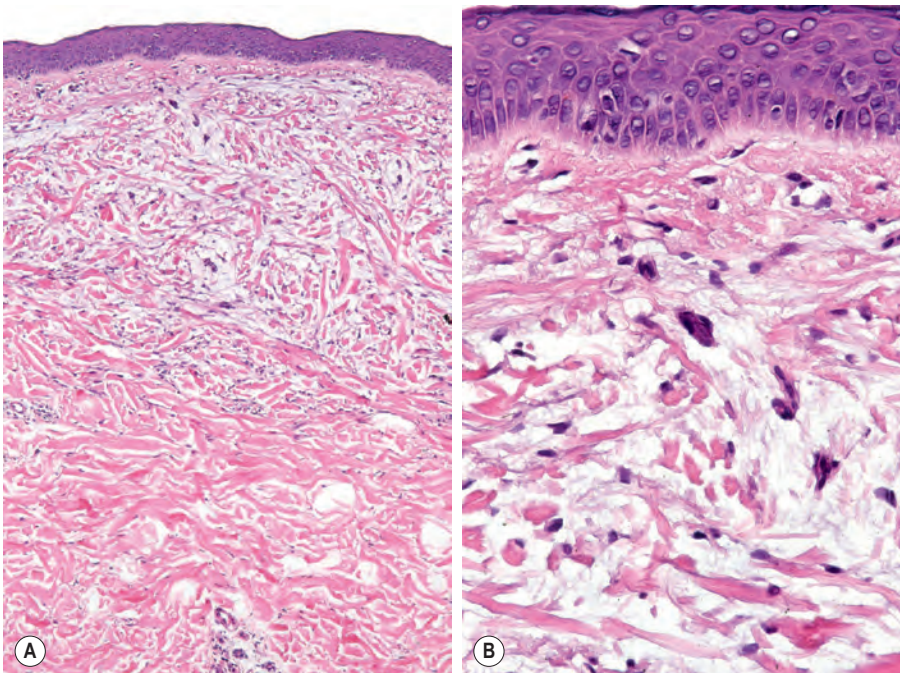
Figure 7-42. Scleredema. (From Elston D, et al. Dermatopathology, 2nd Ed. Elsevier. 2013)

**Table 7-24.** “SLAM” DDX: Malignant Dermal Spindle Cell Tumor “Slammed” Up Against the Epidermis

Disease	Essential Features	Immunostaining Profile
<b>SCC</b> (spindle cell type)	Overlying epidermal keratinocytic atypia	<b>Cytokeratin+</b> (CK5/6, CK903 and MNF116 are most sensitive), <b>p63+</b> , <b>p40+</b> (most specific marker for SCC vs. AFX)
<b>Leiomyosarcoma</b>	Hyperchromatic spindle cells w/ <b>fascicular architecture</b> and <b>cigar-shaped nuclei</b> w/ <b>perinuclear vacuoles (glycogen)</b>	<b>SMA+</b> , <b>Desmin+</b>
<b>AFX</b>	<b>Bizarre/atypical mitotic figures</b> ; mixture of cell types ( <b>multinucleated GCs</b> , histiocyte-like cells, foam cells, and <b>spindle cells</b> )	AFX is a diagnosis of exclusion! <b>Most importantly, must be negative for:</b> Cytokeratin, p63, p40, S100, SOX-10, and Desmin (caution: SMA may have “tram track”/myofibroblast-like staining in AFX) <b>Most useful positive stains:</b> <b>CD10+</b> (also positive in many spindle cell SCCs), Procollagen-1+ <b>Other positive stains:</b> CD68+, CD74+ (weak in AFX, strong in UPS), CD99+ and CD117+ (latter two stains are non-specific)
<b>Melanoma</b> , (desmoplastic/spindle cell type)	Atypical junctional melanocytic proliferation (often subtle), solar elastosis, <b>blue-gray myxoid stroma</b> , and <b>nodular lymphocyte aggregates</b>	<b>S100+</b> , <b>SOX-10+</b> (differentiates from scar), and <b>p75/NGFR+</b> (useful for S100 <sup>-</sup> desmoplastic melanomas)



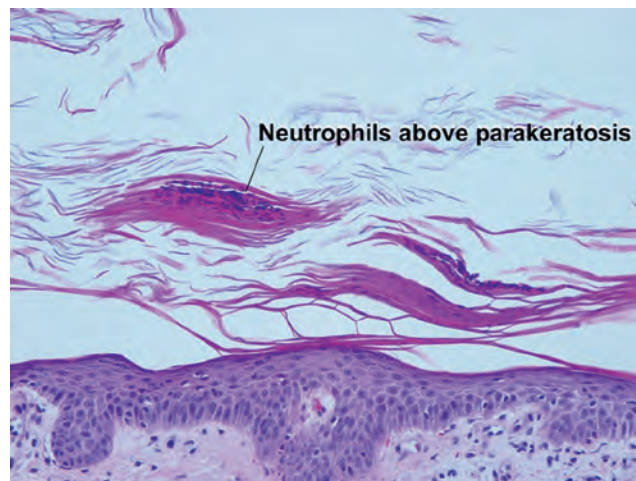
**Figure 7-43.** Morphea. Sclerosis of collagen fibers centered in the deep reticular dermis. At scanning magnification, the junction between the reticular dermis and subcutaneous fat is often smoother and more prominent (line sign). Perivascular lymphocytes, including plasma cells, encircle blood vessels in the reticular dermis, subcutis, and characteristically, the juncture between these two compartments. (From Busam KJ. Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology, 2e. Elsevier. 2015)



**Figure 7-44.** (A, B) Lichen myxedematosus: the collagen fibers are widely separated by mucin deposits. Fibroblasts are increased in number. (From Calonje E, et al. McKee's Pathology of the Skin, 4th Ed. Elsevier. 2011)

**Table 7-25.** Psoriasiform and Spongiotic Disorders

<b>Plaque Psoriasis</b>	<b>Regular (“psoriasiform”) acanthosis, neutrophil microabscesses</b> in stratum corneum (Munro) and spinosum (Kugoj), <b>hypogranulosis, confluent parakeratosis</b> , suprapapillary plate thinning, dilated vessels in dermal papillae, and little or no serum crust
<b>Guttate Psoriasis</b>	Minimal acanthosis, <b>mounds of neutrophils w/ underlying parakeratosis</b> (thicker and more adherent than pityriasis rosea) (Fig. 7-45)
<b>Pustular Psoriasis</b>	<b>Sub- and intracorneal neutrophilic abscesses</b>
<b>Lichen Simplex Chronicus</b>	<b>Irregular acanthosis, hypergranulosis</b> , and vertical collagen in dermal papillae; lacks neutrophilic microabscesses
<b>MF</b>	<b>Hyperchromatic, cerebriform epidermotropic lymphocytes w/ perinuclear halo</b> (“lumps of coal on a pillow”); <b>minimal spongiosis</b> relative to number of lymphocytes in epidermis, <b>band-like superficial dermal lymphocytic infiltrate</b> w/ minimal to no inflammation deep to superficial vessels (“ <b>bare underbelly sign</b> ”), lymphocytes “ <b>tagging</b> ” <b>basal layer of epidermis</b> (“pigs lining up at the trough”), <b>wiry papillary dermal fibrosis</b> , and lacks intraepidermal neutrophils (Fig. 7-46)
<b>PRP</b>	<b>Hyperkeratosis</b> out of proportion to degree of acanthosis, “ <b>checkerboard</b> ” <b>parakeratosis</b> (parakeratosis horizontally and vertically alternating w/ orthohyperkeratosis), <b>follicular plugging</b> , “ <b>shoulder parakeratosis</b> ” (around follicular ostia), <b>focal acantholysis</b> (helpful clue), and <b>thickened suprapapillary plates</b> ; <b>NO NEUTS!</b> (Fig. 7-47)
<b>Secondary Syphilis</b>	Psoriasiform hyperplasia ( <b>long, sexy, slender, rete</b> ); “ <b>dirty</b> ” <b>lichenoid inflammation</b> w/ neutrophils and <b>plasma cells</b> , lymphocyte exocytosis, and swollen endothelial cells CAUTION: has neutrophils in horn!
<b>Subacute Spongiotic Dermatitis</b>	Mild to moderate acanthosis +/- parakeratosis, <b>prominent spongiosis</b> , <b>Langerhans cell “microabscesses”</b> in spinous layer (esp. allergic contact dermatitis) CAUTION: neutrophils may be seen but are limited to areas of serum crust; lacks intraspinous neutrophil microabscesses
<b>Pityriasis Rosea</b>	Subacute spongiotic dermatitis w/ <b>thin mounds of parakeratosis</b> (lacks neutrophils seen in psoriasis), and <b>extravasated RBC’s</b> around superficial dermal vessels (Fig. 7-48)
<b>ILVEN</b>	<b>Horizontally alternating</b> orthokeratosis (WITH granular layer) and parakeratosis (WITHOUT granular layer)
<b>Tinea</b>	Epidermal changes may resemble psoriasis or spongiotic dermatitis → clue: “ <b>layered</b> ” <b>stratum corneum</b> (compact stratum corneum immediately above granular layer), “ <b>Bullet holes</b> ” (hyphae) in compact keratin, and sub/intracorneal neutrophil abscesses
<b>Nutritional Deficiency Dermatitis</b>	Psoriasiform hyperplasia w/ confluent parakeratosis AND <b>pallor of upper 1/3 of epidermis</b> (Fig. 7-49)



**Figure 7-45.** Guttate psoriasis. (From Elston D, et al. Dermatopathology, 2nd Ed. Elsevier. 2013)



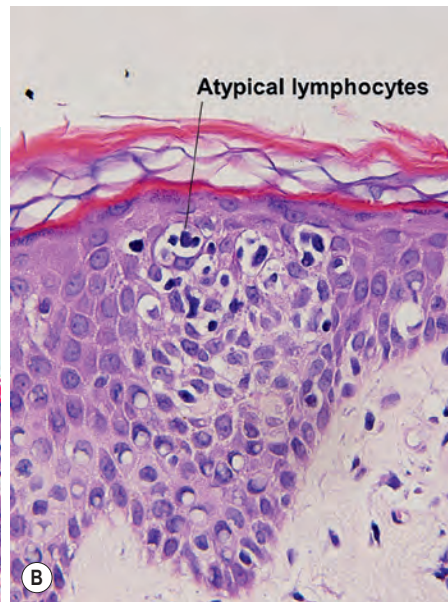
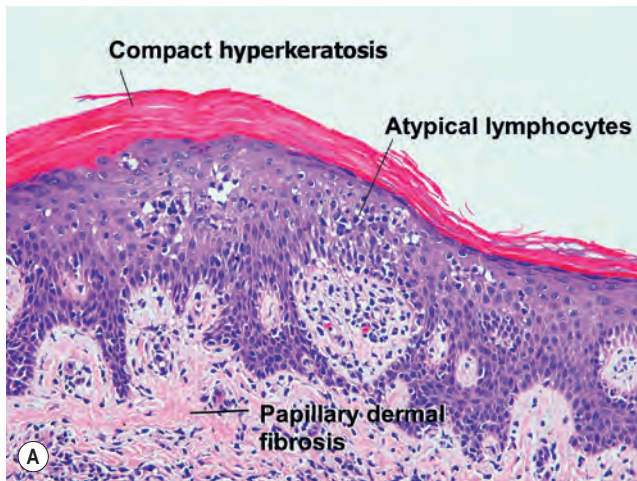


Figure 7-46. Psoriasiform mycosis fungoides. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

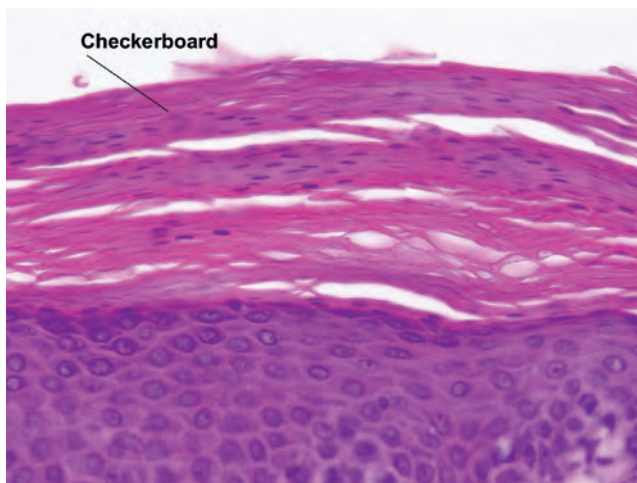


Figure 7-47. Pityriasis rubra pilaris. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

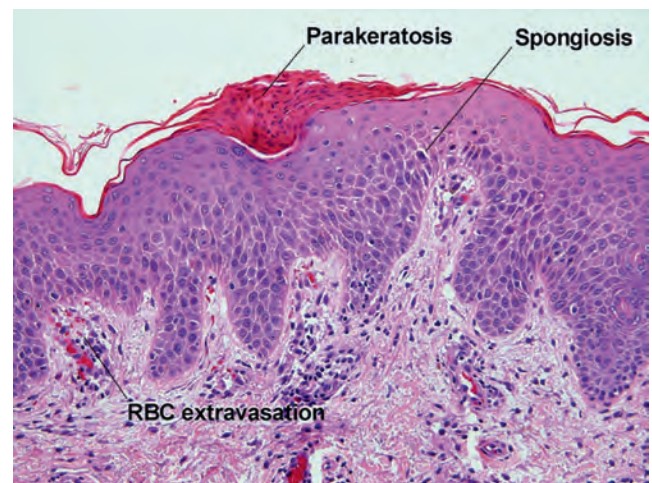


Figure 7-48. Pityriasis rosea. RBC, red blood cell. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

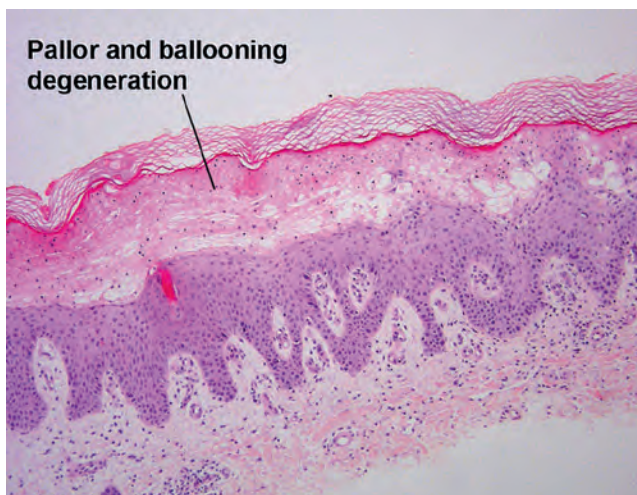


Figure 7-49. Nutritional deficiency. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

#### Box 7-2. Mnemonic

"Neuts in the horn (stratum corneum) = **PTICSS**"

**P**soriasis, **T**inea, **I**mpetigo, **C**andida, **S**eborrheic dermatitis, **S**yphilis

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

#### Box 7-3. Mnemonic

"Subcorneal pustules = **CAT PISS**"

**C**andida, **A**cropustulosis of infancy, **T**ransient neonatal pustular melanosis, **P**ustular psoriasis, **I**mpetigo, **S**neddon-Wilkinson (and IgA pemphigus), **S**taph scalded skin

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



Table 7-26. Acantholytic Disorders

Disease	H&E	DIF	Notes
Pemphigus foliaceus	<b>Subcorneal split</b> , acantholysis in granular layer like “shingles blowing off of a roof”	Intercellular IgG and C3	As a result of anti-Dsg1 antibodies Most important Ddx is staph scalded skin → DIF distinguishes
Pemphigus vulgaris	<b>Suprabasal split</b> , “tombstoning of basal layer,” and <b>acantholysis extends down hair follicles</b>	Same as pemphigus foliaceus, but w/ ↑staining in lower half of epidermis	As a result of anti-Dsg1 and anti-Dsg3 antibodies (Fig. 7-50)
Pemphigus vegetans	PEH w/ <b>eosinophilic abscesses</b> in epidermis; subtle suprabasal clefting	Pemphigus pattern (intercellular IgG and C3)	Simply a clinical variant of PV
Pemphigus erythematosus	Similar to <i>P. foliaceus</i>	<b>BMZ</b> (linear to granular) + <b>intercellular pemphigus pattern</b>	Overlap of pemphigus foliaceus and cutaneous lupus erythematosus Anti-desmoglein 1 and ANA+
Paraneoplastic pemphigus	Combination of <b>suprabasal acantholysis</b> and <b>interface dermatitis</b>	DIF similar to <i>P. erythematosus</i> IIF+ on rat bladder epithelium	<b>Antiplatelet</b> family antibodies detected w/ immunoblotting (including anti-BP-230!) May be a/w B-cell lymphoproliferative disorders, thymoma, Castleman's disease, some carcinomas, sarcomas, and even melanoma
Hailey-Hailey	<b>Epidermal hyperplasia</b> , full-thickness intraepidermal acantholysis (“ <b>dilated brick wall</b> ”), mild dyskeratosis, and k'cytes have <b>distinct pink-red cytoplasm</b>	Negative	Less dyskeratosis compared with Darier's (Fig. 7-51)
Darier's disease	<b>Acantholytic dyskeratosis</b> usually with suprabasal clefting	Negative	Dyskeratosis manifests as <b>corps ronds/ grains</b> (Fig. 7-52)
Grover's disease	Focal changes in either pemphigus-like, Darier-like, or Hailey-Hailey-like pattern	Negative	May have mix of all three patterns; CPC required
Warty dyskeratoma	<b>Endophytic</b> w/ either <b>cup shape</b> or resembling hair follicle; <b>prominent acantholytic dyskeratosis</b> with cells expelled into the center of the crater leaving dermal papillae looking like “villi”	Negative	Solitary nature and cup-shaped architecture are the most helpful clues to distinguish from Darier's

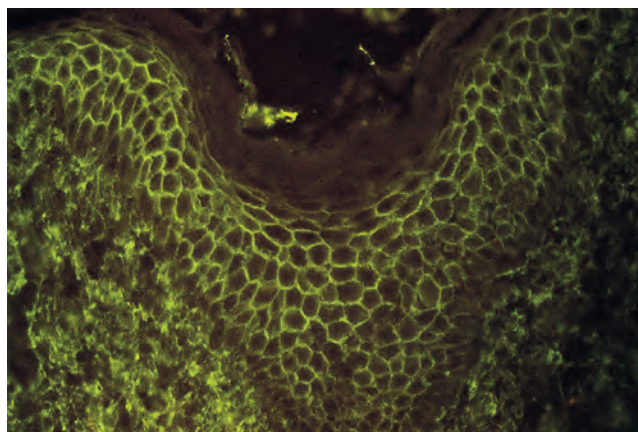


Figure 7-50. Pemphigus vulgaris. (From Weedon D. Weedon's Skin Pathology, 3rd Ed. Elsevier. 2009)

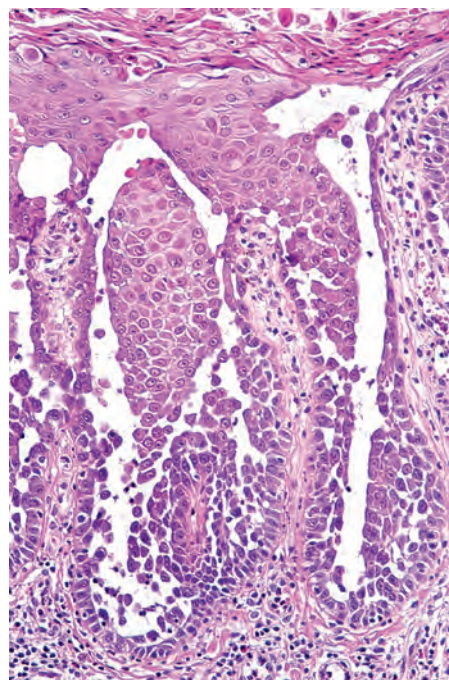
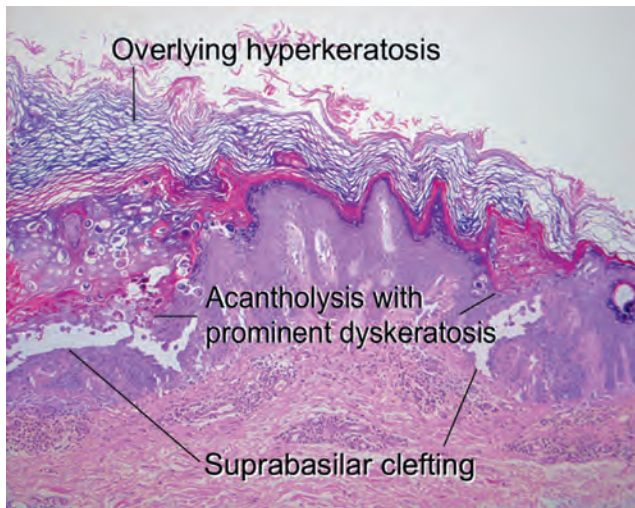


Figure 7-51. Hailey-Hailey disease: in contrast to Darier's disease, dyskeratosis is usually minimal or even absent. (From Calonje E, et al. McKee's Pathology of the Skin, 4th Ed. Elsevier. 2011)



**Figure 7-52.** Darier's disease. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

#### Box 7-4. Mnemonic

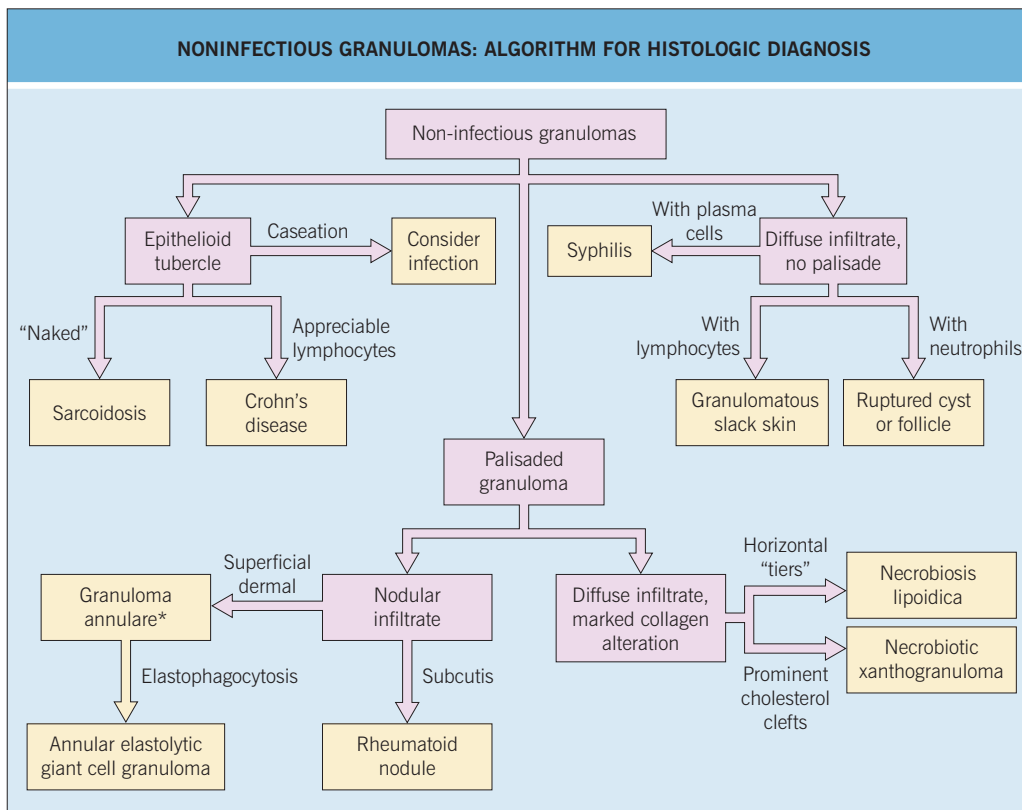
"Eosinophilic spongiosis = **HAAPPIED**"

**H**erpes gestationis, **A**rthropod, **A**llergic contact, **P**emphigus, **P**emphigoid, **I**ncontinentia pigmenti, **E**rythema toxicum neonatorum, **D**rug reaction (HAAPPIED)

(From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

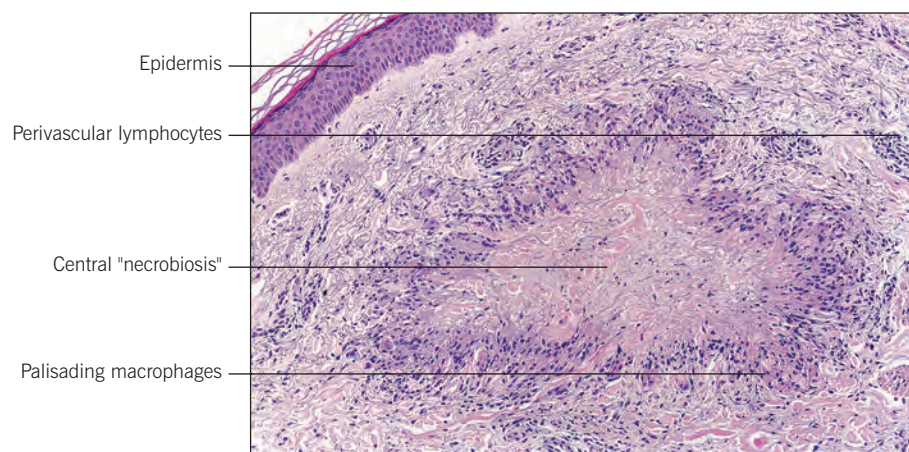
**Table 7-27.** High-Yield Granulomatous Disorders (Fig. 7-53)

<b>GA (Interstitial)</b>	Patchy interstitial histiocytes, ↑mucin, lymphocytes, and ↑eosinophils
<b>GA (Palisaded)</b>	Palisaded histiocytes in <b>superficial-mid dermis</b> (except deep GA) encircling and degrading collagen fibers; increased dermal <b>mucin</b> ; <b>↑eosinophils</b> (Fig. 7-54)
<b>Gout</b>	Palisaded granuloma around light pink/gray feathery <b>needle-shaped crystals</b> (best seen if fixed in ethanol) (Fig. 7-55)
<b>Lupus Miliaris Disseminata Faciei</b>	Caseating necrosis (amorphous pink debris) surrounded by histiocytes on facial skin
<b>NLD</b>	Layered pan-dermal granulomatous inflammation and necrobiosis ("layered lasagna"), entire dermis appears altered, with "square biopsy" sign (Fig. 7-56)
<b>NXG</b>	X-shaped red zones of necrosis w/ nuclear debris within granulomas; cholesterol clefts and <b>bizarre, HUGE multinucleate giant cells</b> (often with 50-100 nuclei in horseshoe or osteoclast-like pattern) (Fig. 7-57)
<b>Rheumatoid Nodule</b>	Deep dermal-SQ palisaded granuloma surrounding pink fibrin; no mucin (Fig. 7-58)
<b>Sarcoid</b>	<b>Well-formed epithelioid granulomas</b> w/ minimal surrounding lymphocytic inflammation ("naked"); often difficult to distinguish from Crohn's disease, Melkersson-Rosenthal syndrome, zirconium and beryllium deposition, perioral dermatitis, and tuberculoid leprosy (Fig. 7-59)

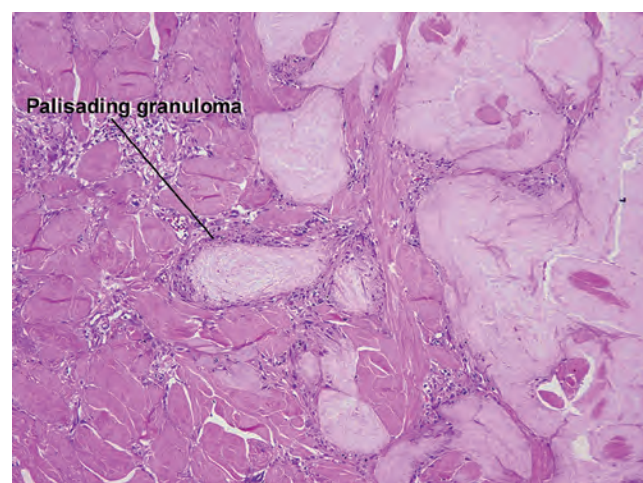


**Figure 7-53.** Noninfectious granulomas: algorithm for histologic diagnosis. Interstitial granulomatous dermatitis and palisaded neutrophilic and granulomatous dermatitis may represent an additional diagnostic consideration. May also have a patchy dermal interstitial pattern without palisades, or subcutaneous palisades, with more mucin than rheumatoid nodules. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

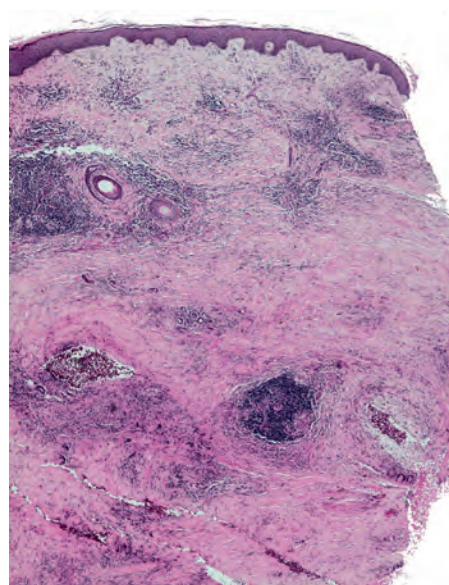




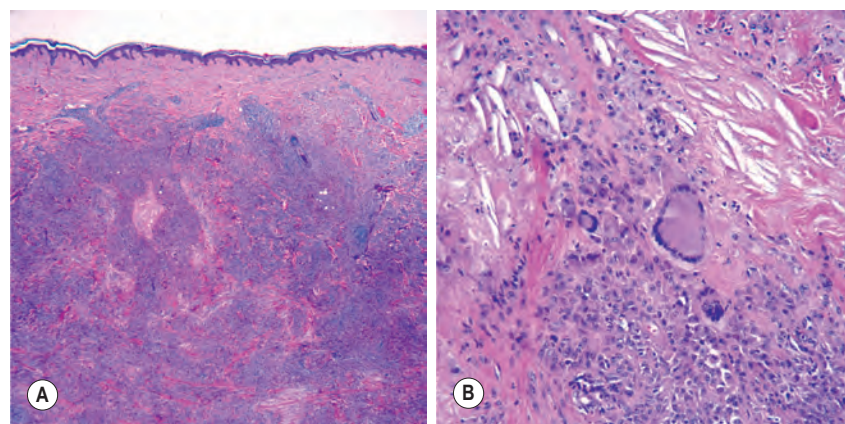
**Figure 7-54.** Granuloma annulare (low mag). (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)



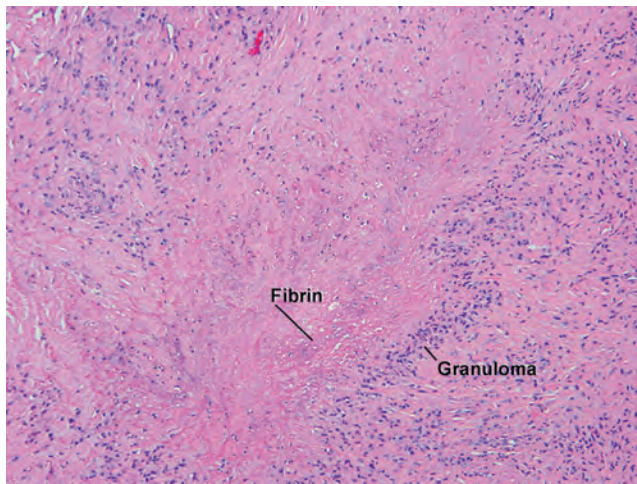
**Figure 7-55.** Gout. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



**Figure 7-56.** Necrobiosis lipoidica. (From Weedon D. *Weedon's Skin Pathology*, 3rd Ed. Elsevier. 2009)



**Figure 7-57.** Necrobiotic xanthogranuloma. Low power **(A)** showing pan-dermal granulomatous inflammation. High power **(B)** demonstrates cholesterol clefts and bizarre, large multinucleated histiocytic giant cells. (From Weedon D. *Weedon's Skin Pathology*, 3rd Ed. Elsevier. 2009)



**Figure 7-58.** Rheumatoid nodule. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



**Figure 7-59.** Sarcoidosis. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

**Table 7-28.** Histologic Features of the Major Granulomatous Dermatitides

	Sarcoidosis	Granuloma Annulare	Necrobiosis Lipoidica	AEGCG	Cutaneous Crohn's Disease	Rheumatoid Nodule	Interstitial Granulomatous Dermatitis	Palisading Neutrophilic and Granulomatous Dermatitis
Typical location	Superficial and deep dermis*	Superficial and mid dermis*	Entire dermis, subcutis	Superficial and mid dermis	Superficial and deep dermis	Deep dermis, subcutis	Mid and deep dermis	Entire dermis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial	Diffuse palisading and interstitial; horizontal "tiers"	Palisading, irregular	Tubercle with surrounding lymphocytes	Palisading	Palisading in small "rosettes"	Palisading; <b>prominent neutrophils and leukocytoclasia</b>
Necrobiosis (altered collagen)	No	Yes ("blue")	Yes ("red")	No	No	Yes ("red")	Yes ("blue")	Yes ("blue")
Giant cells	Yes	Variable	Yes	Yes	Yes	Yes	Variable	Variable
Elastolysis	No	Variable	Variable	<b>Yes</b>	No	No	Variable	Variable
Elastophagocytosis	No	No	No	<b>Yes</b>	No	No	No	No
Asteroid bodies	Yes	Variable	Variable	Yes	No	No	Variable	Variable
Mucin	No	<b>Yes</b>	Minimal	No	No	Variable	Minimal	Variable
Extracellular lipid	No	Variable	Yes	No	No	Variable	No	No
Vascular changes	No	Variable	<b>Yes</b>	No	No	Yes	No	Yes

\*Subcutaneous variant can also occur (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

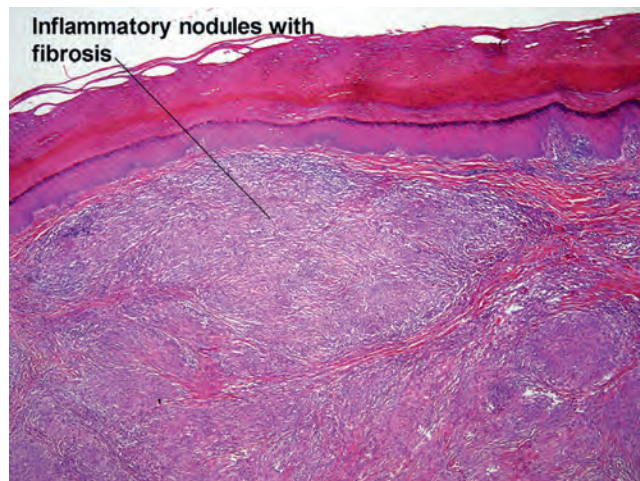
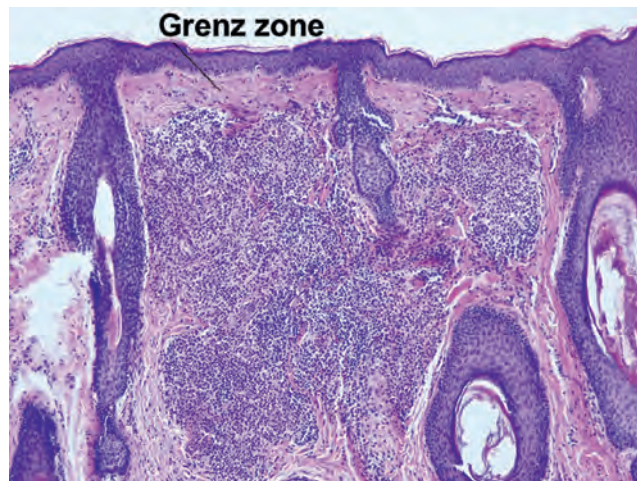


**Table 7-29.** High-Yield Inflammatory and Occlusive Vascular Disorders**Vasculitides (Vessel Inflammation and Destruction, Fibrin in Vessel Wall, RBC Extravasation, and Leukocytoclasia)**

Henoch-Schönlein purpura	LCV, IgA in vessel walls (DIF)
Mixed cryoglobulinemia	LCV
Granulomatosis with polyangiitis (Wegner's)	LCV involving vessels high up (postcapillary venules) and down low (medium-sized vessels) → may evolve into palisading granuloma w/ giant cells surrounding neutrophil-rich abscess, <b>+/- granulomatous vasculitis</b>
Churg-Strauss	LCV involving vessels up high (postcapillary venules) and down low (medium-sized vessels) → may evolve into palisading granuloma w/ central degranulating eosinophils and flame figures, <b>+/- granulomatous vasculitis</b>
Erythema Elevatum Diutinum	LCV w/ numerous eosinophils, <b>"onion-skin" fibrosis</b> , and nonfacial location (Fig. 7-60)
Granuloma faciale	LCV w/ numerous eosinophils, plasma cells and histiocytes, <b>Grenz zone</b> , mild fibrosis (<EED), and most commonly on face (Fig. 7-61)

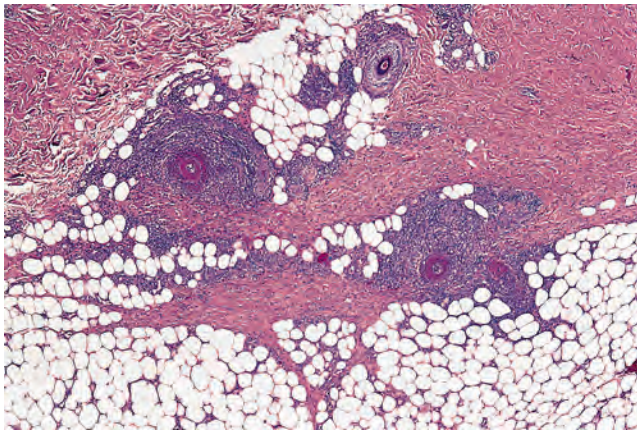
**Occlusive Vasculopathies ("Plugged" Vessels W/ Minimal Primary Vascular Inflammation)**

Thrombotic	<b>Intravascular thrombus</b> Causes: cryoglobulinemia type I, coumadin necrosis, DIC, lupus anticoagulant, factor V Leiden mutation, and protein C or S deficiency → all are histologically indistinguishable
Livedoid vasculopathy	<b>Bright pink-red hyalinized vessel walls</b> ("red crayon-like"), <b>intravascular thrombosis</b> of superficial dermal vessels, and background <b>stasis</b> changes
Calciphylaxis	<b>Calcified vessel walls w/ thrombosis</b> deep in the <b>fat</b> , +/- extravascular calcium debris
Levamisole-associated vasculopathy	Mixed features of <b>LCV</b> + small vessel <b>thrombosis</b> high in dermis Patients also have neutropenia and <b>P- and/or C-ANCA antibodies</b>

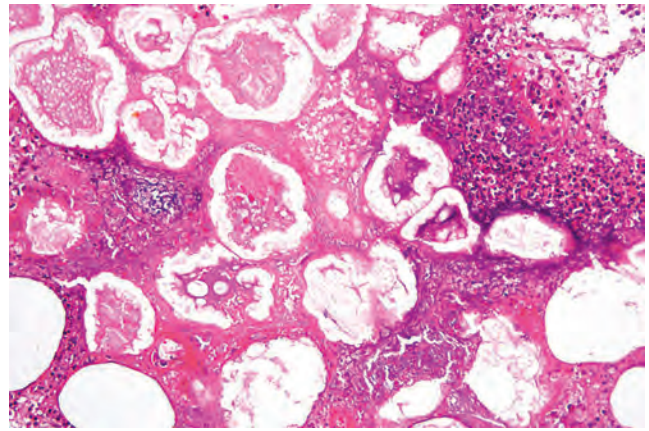
**Figure 7-60.** Erythema elevatum diutinum with extensive fibrosis. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)**Figure 7-61.** Granuloma faciale. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)

**Table 7-30.** High-Yield Panniculitides

<b>Cold Panniculitis (Deep Perniosis)</b>	<b>Lobular fat necrosis</b> w/ lymphocytes, histiocytes, and neuts at dermo-pannicular junction; +/- overlying dermal perniois
<b>Erythema Induratum/Nodular Vasculitis</b>	<b>Caseous necrosis of fat lobules</b> (neutrophil-rich) + <b>vasculitis</b> of small and medium (PAN-sized) lobular and septal vessels + <b>septal thickening</b> Major clue: involves lobules and septae diffusely, whereas PAN involves one lobule and only damages fat immediately surrounding the affected vessel
<b>Erythema Nodosum</b>	<b>Septal panniculitis</b> with <b>neutrophils</b> in septum (early) → progresses to <b>septal thickening</b> w/ small granulomas with central clefting ( <b>Miescher's granulomas</b> ) Note: there is only slight spill-over of inflammation into the lobules
<b>Lupus Panniculitis</b>	<b>Lobular fat necrosis</b> w/ <b>pink hyalinization</b> around fat, <b>nodular PV/PA lymphoplasmacytic aggregates</b> , +/- ↑mucin and interface dermatitis
<b>Sclerema Neonatorum</b>	<b>Lobular panniculitis</b> w/ <b>radiating needle-shaped crystals</b> within adipocytes; lacks surrounding granulomatous inflammation
<b>SQ Fat Necrosis of Newborn (and Poststeroid Panniculitis)</b>	<b>Lobular panniculitis</b> w/ <b>radiating needle-shaped crystals</b> within adipocytes w/ associated brisk granulomatous inflammation
<b>PAN</b>	<b>Vasculitis of solitary medium-sized vessel</b> (artery) in <b>deep dermis/SQ</b> with fibrin in vessel wall and obliteration of lumen, <b>mild lobular panniculitis</b> in area adjacent to affected vessel (Fig. 7-62)
<b>Pancreatic Panniculitis</b>	<b>Lobular panniculitis</b> w/ <b>pink-purple</b> blobs in fat lobules representing enzymatic fat necrosis ("ghost cells") (Fig. 7-63)
<b>Lipodermatosclerosis (Stasis Panniculitis)</b>	<b>Lobular panniculitis</b> w/ <b>cystic fat necrosis</b> w/ <b>lipomembranous</b> change ("frost on a window pane"), septal fibrosis, lipophages, and <b>overlying stasis changes</b>



**Figure 7-62.** Cutaneous polyarteritis nodosa. The affected small arteries in the upper subcutis show marked fibrin extravasation into their walls. (From Weedon D. *Weedon's Skin Pathology*, 3rd Ed. Elsevier. 2009)

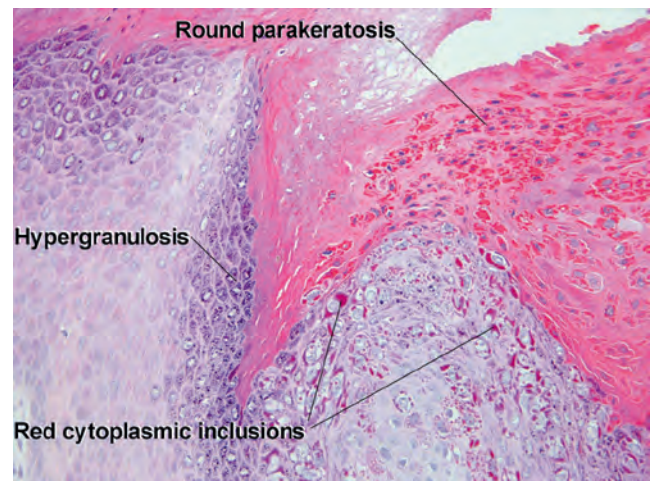


**Figure 7-63.** Pancreatic panniculitis. Characteristic "ghost" cells and basophilic calcification. (From Brinster NK et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier. 2011)

## Infectious processes

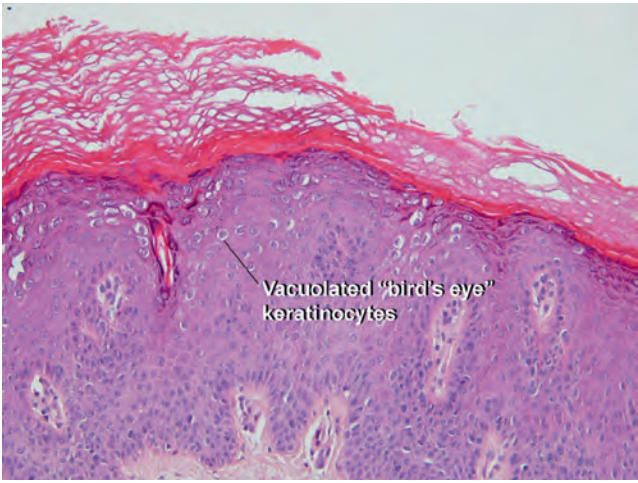
- HPV-induced lesions
  - Verruca vulgaris
  - Myrmecia (Fig. 7-64)
  - Verruca plana (Fig. 7-65)
  - Verruca plana with EDV change (Fig. 7-66)
  - Verrucous carcinoma (Fig. 7-67)
- Histiocytic inclusions: His GIRL Penelope-  
Histoplasmosis, Granuloma Inguinale,  
Rhinoscleroma, Leishmaniasis/Leprosy,  
Penicillium
- Infections with endospores: rhinosporidiosis  
("spores as big as a rhino") (Fig. 7-68);  
coccidioidomycosis (Fig. 7-69)

Text continued on p. 414

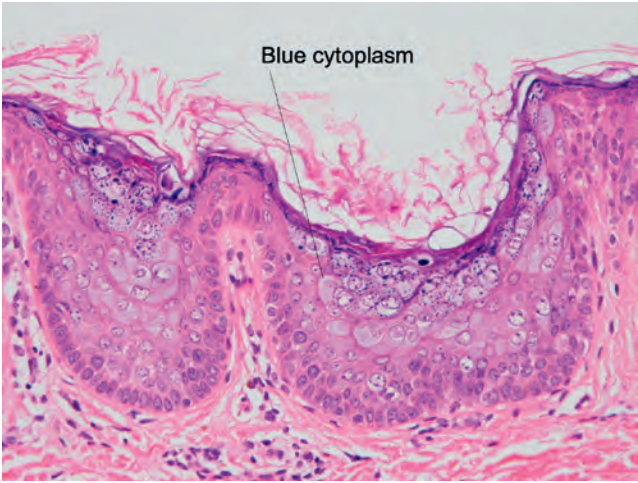


**Figure 7-64.** Myrmecia. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)





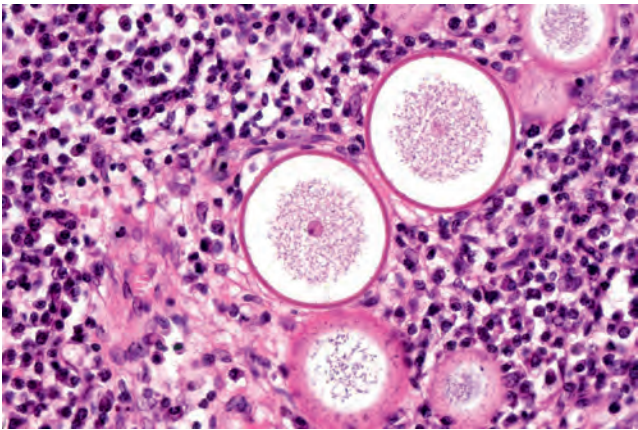
**Figure 7-65.** Verruca plana. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



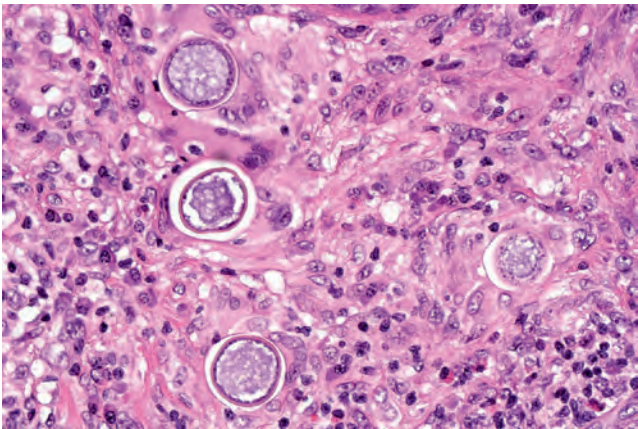
**Figure 7-66.** Verruca plana with changes characteristic of epidermodysplasia verruciformis. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



**Figure 7-67.** Verrucous carcinoma. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



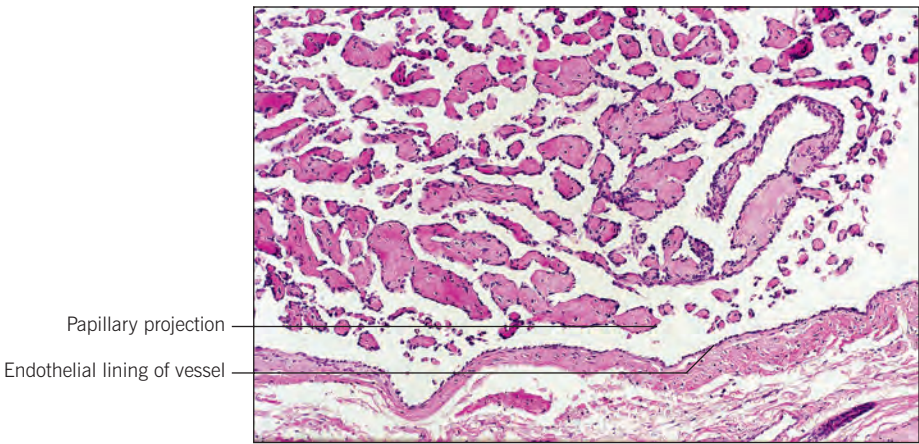
**Figure 7-68.** Rhinosporidiosis: individual spores mature to form small trophic cysts. (From Calonje E, et al. *McKee's Pathology of the Skin*, 4th Ed. Elsevier. 2011)



**Figure 7-69.** Coccidioidomycosis: multiple spherules are present with surrounding chronic inflammation. (Courtesy of J. Cohen, MD, Dermatopathology Laboratory, Tucson, USA.)

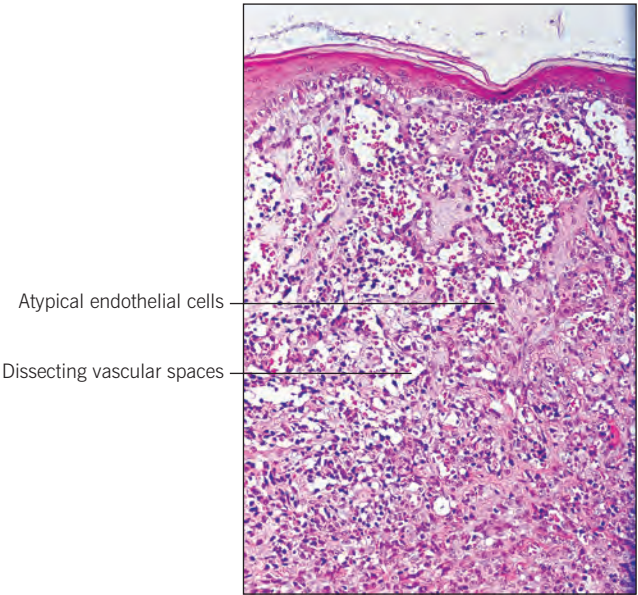
Table 7-31. High-Yield Neural Tumors	
Neurofibroma (NF)	"Sea gull"-shaped <b>wavy nuclei</b> in <b>bubble gum pink stroma</b> ; scattered mast cells
Plexiform Neurofibroma	Wavy fascicles of NF embedded in myxoid background of diffuse NF
Schwannoma	<b>Encapsulated SQ nodule</b> , <b>Antoni A/B areas</b> , <b>hyalinized ectatic vessels</b> within tumor
Palisaded Encapsulated Neuroma	Well-circumscribed, pseudoencapsulated <b>superficial dermal nodule</b> comprised of <b>nerve fascicles</b> separated by clefts
Traumatic Neuroma	Small <b>nerve fascicles</b> surrounded by <b>scar</b> tissue
Nerve Sheath Myxoma ("Neurothekeoma")	Myxoid lobules of spindled cells in dermis surrounded by fibrous septa



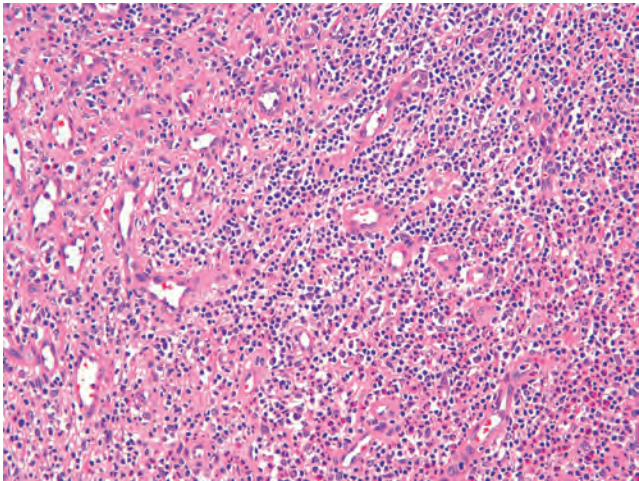


**Figure 7-70.** Intravascular papillary endothelial hyperplasia (high mag). (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)

Table 7-32. High-Yield Vascular Tumors	
<b>Masson's/IPEH</b>	<b>Papillary projections</b> of bland endothelial cells around hyaline cores; <b>well-circumscribed</b> (not a feature seen in malignant vascular neoplasms); <b>arises within large thrombosed vessel</b> (Fig. 7-70)
<b>Angiosarcoma</b>	Poorly formed vessels filled with RBC's and lined by <b>large, dark, atypical endothelial cells</b> that protrude into the lumen in a "piled-on" fashion; <b>NOT well circumscribed</b> (Fig. 7-71)
<b>Glomeruloid Hemangioma</b>	Round nodules comprised of <b>capillaries contained within a large dilated vascular space</b> in the dermis → resembles renal glomerulus; part of POEMS syndrome
<b>Angiolymphoid Hyperplasia with Eosinophilia</b>	<b>Lymphoid nodules</b> + TONS of <b>eosinophils</b> around thick-walled vessels with large " <b>epithelioid</b> " endothelial cells often w/ intracytoplasmic vacuoles (Fig. 7-72)
<b>Kaposi Sarcoma</b>	<b>Bloody "busy dermis,"</b> spindled cells with adjacent <b>slit-like vessels</b> , " <b>promontory sign</b> " (vessels forming around vessels), and ↑ <b>plasma cells</b>



**Figure 7-71.** Angiosarcoma (low mag). (From Rapini R. *Practical Dermatopathology*, 2nd Ed. Elsevier. 2012)



**Figure 7-72.** Angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma). Nodular proliferation of vessels lined by plump epithelioid endothelial cells. A florid inflammatory infiltrate of lymphocytes and eosinophils is present. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd Ed. Elsevier. 2015)



**Table 7-33.** High-Yield Adipocytic Tumors

Disease	Key Features
Lipoma	Solely mature lipocytes w/ small eccentric nucleus
Mobile encapsulated lipoma	Lobules of <b>necrotic</b> fat enclosed within <b>fibrous capsule</b>
Angiolipoma	Lipoma with capillary proliferation; capillaries filled w/ fibrin thrombi
Pleomorphic lipoma	Mature lipocytes among <b>myxoid</b> matrix with interspersed <b>ropey collagen</b> , bland spindle cells, and <b>floret giant cells</b>
Spindle cell lipoma	Mature lipocytes among <b>myxoid matrix</b> containing <b>spindle cells</b> and interspersed <b>ropey collagen</b> ; <b>CD34+</b>
Hibernoma	<b>Multivacuolated</b> tumor cells, not as pink or grainy-appearing as granular cell tumor
Nevus lipomatosus superficialis	Mature lipocytes infiltrating the superficial dermis; similar, but more extreme features seen in Goltz syndrome

**Table 7-34.** High-Yield Smooth Muscle DDx

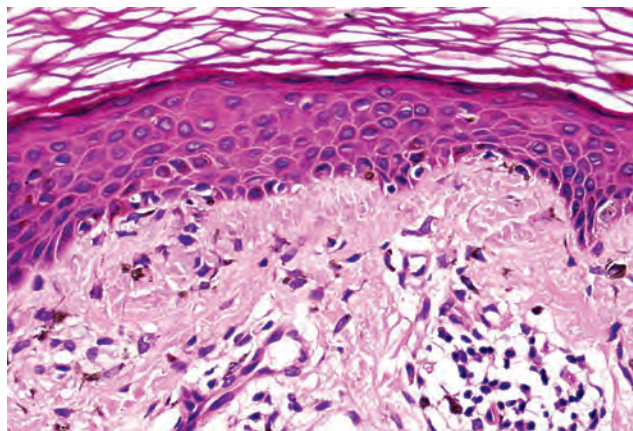
<b>Accessory Nipple</b>	Central pore-like structure, deep <b>mammary</b> (modified apocrine) <b>glands</b> and scattered smooth muscle bundles
<b>Becker's Nevus</b>	Looks like <b>epidermal nevus</b> + <b>smooth muscle hamartoma</b> together w/ <b>terminal hairs</b>
<b>Piloileiomyoma</b>	<b>Haphazardly arrayed</b> smooth muscle fascicles in <b>superficial-mid dermis</b>
<b>Angioleiomyoma</b>	<b>Round</b> , pink nodule with compressed vascular lumen in <b>deep dermis/SQ</b>
<b>Leiomyosarcoma</b>	Hypercellular proliferation of spindled smooth muscle cells w/ <b>atypical</b> , <b>hyperchromatic nuclei</b> and mitoses

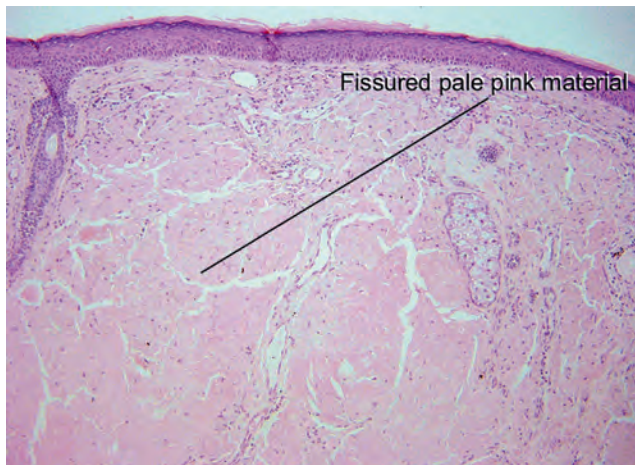
**Table 7-36.** Amorphous "Pink Stuff in Dermis" DDx

<b>Amyloid (Macular/Lichen)</b>	Sparse pink deposits of amyloid ( <b>AK type</b> ) in superficial dermis, <b>melanophages</b> , <b>no inflammation</b> (Fig. 7-73)
<b>Amyloid (Nodular)</b>	<b>Fissured</b> , pale pink amyloid ( <b>AL type</b> ) material in superficial to mid dermis, and <b>abundant plasma cells</b> (distinguishes from colloid milium) (Fig. 7-74)
<b>Colloid Milium</b>	<b>Fissured</b> , pale pink deposits <b>completely filling/expanding superficial-mid dermis</b> (deeper than macular/lichen amyloid); extensive <b>solar elastosis (adult form only)</b> ; <b>no inflammation</b> (vs nodular amyloid) (Fig. 7-75)
<b>Erythropoietic Protoporphyrria</b>	<b>Hyaline cuff</b> around superficial vessels, no solar elastosis (because patients diligently avoid sun) (Fig. 7-76)
<b>Lipoid Proteinosis</b>	Pink <b>hyaline BMZ material</b> (type IV collagen; PAS-D+) predominantly centered around superficial and <b>deep</b> (deeper than EPP) vessels and adnexae, with <b>"onion skin"</b> pattern (Fig. 7-77)

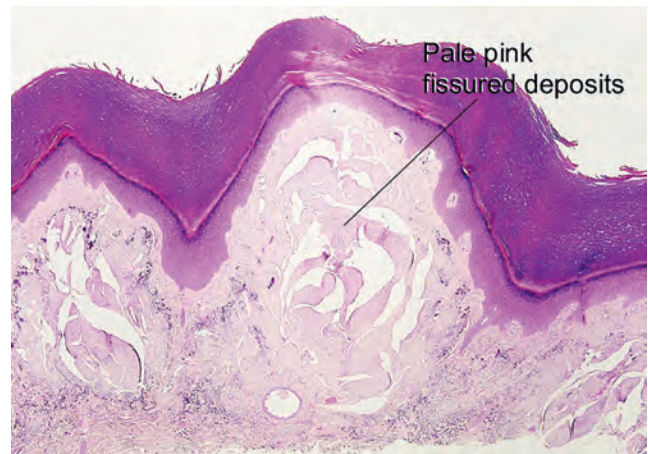
**Table 7-35.** DF vs. DFSP vs. Fibromatosis

<b>DF</b>	Dermal-based spindle cell neoplasm with <b>"curlicue" pattern</b> , <b>collagen trapping</b> (most obvious at periphery), overlying <b>epidermal/follicular induction</b> , and <b>hemosiderin laden GCs and histiocytes</b> ; +/- significant hemorrhage (aneurysmal DF); <b>never infiltrates deeply into fat!</b> ; <b>factor XIIIa<sup>+</sup></b> , <b>stromelysin-3<sup>+</sup></b> , and <b>CD34<sup>-</sup></b>
<b>DFSP</b>	Densely cellular <b>dermal and SQ tumor w/ storiform</b> pattern, infiltrates deep into SQ fat enveloping lipocytes in a <b>"honeycomb" pattern</b> ; <b>CD34<sup>+</sup></b> , <b>factor XIIIa<sup>+</sup></b> , <b>stromelysin-3<sup>+</sup></b> , and <b>t(17;22) translocation</b> (detectable by FISH)
<b>Fibromatosis</b>	<b>Long "sweeping" fascicles</b> of myofibroblasts with <b>wavy corkscrew nuclei</b> and wavy collagen

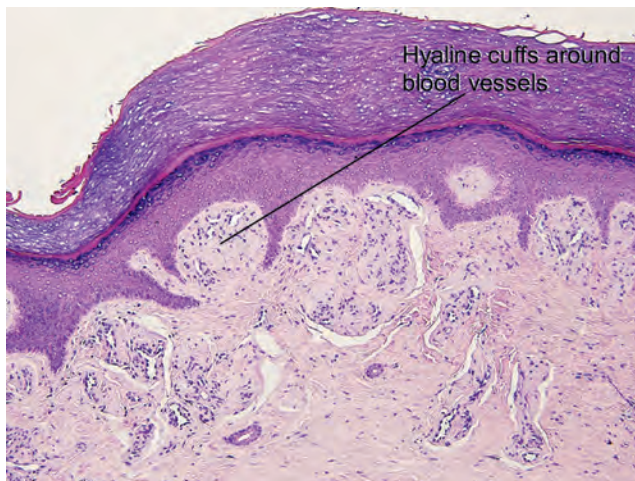
**Figure 7-73.** Macular amyloid. (From Brinster NK et al. Dermatopathology: A Volume in the High Yield Pathology Series. Elsevier, 2011.)



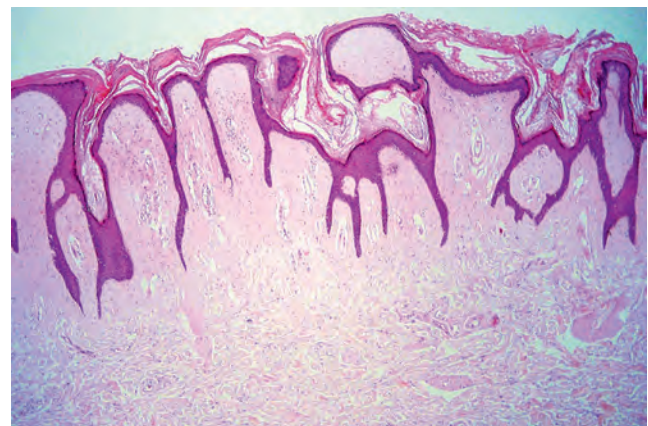
**Figure 7-74.** Nodular amyloid. (From Elston D, et al. *Dermatopathology: Requisites in Dermatology*, 1st Ed. Elsevier. 2008.)



**Figure 7-75.** Colloid milium. (From Elston D, et al. *Dermatopathology: Requisites in Dermatology*, 1st Ed. Elsevier. 2008.)



**Figure 7-76.** EPP. (From Elston D, et al. *Dermatopathology: Requisites in Dermatology*, 1st Ed. Elsevier. 2008.)

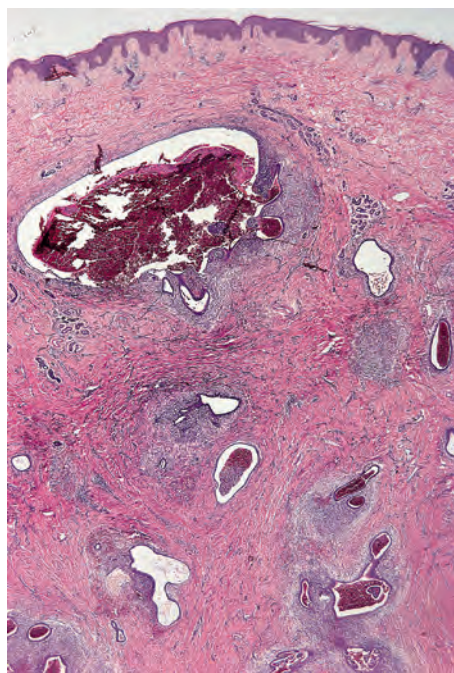


**Figure 7-77.** Lipoid proteinosis. (From Elston D, et al. *Dermatopathology: Requisites in Dermatology*, 1st Ed. Elsevier. 2008.)

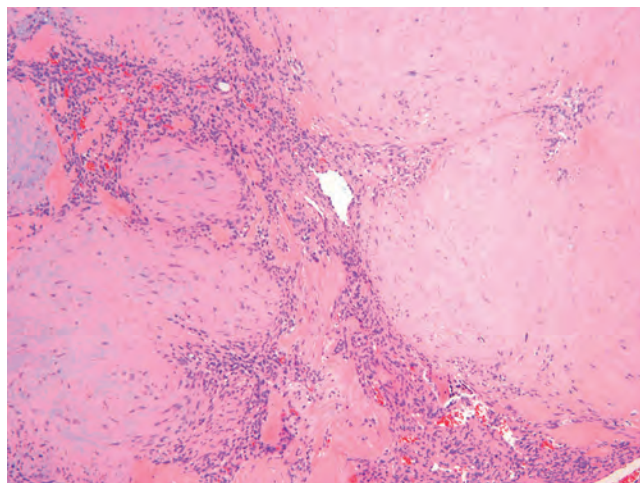
**Table 7-37.** Immediate Pattern Recognition Diagnoses

<b>Chondrodermatitis Nodularis</b>	Ulcer w/ adjacent epidermal acanthosis, underlying reparative change, and <b>eosinophilic degenerated cartilage</b>
<b>Chronicus Helicis</b>	
<b>Cutaneous Endometriosis</b>	Well-formed <b>glands of varying sizes</b> , lined by pseudostratified columnar epithelium and surrounded by <b>endometrial stroma</b> (basaloid cells in fibromyxoid background); <b>RBCs and hemosiderin</b> within and surrounding glands (Fig. 7-78)
<b>Elastosis Perforans Serpiginosa</b>	<b>Elastic fibers</b> (stains black with VVG) spiraling through <b>narrow serpiginous channel</b> in epidermis
<b>Giant Cell Tumor of Tendon Sheath</b>	Deep tumor arising from tendon, containing innumerable multinucleate <b>osteoclast-like giant cells</b> , and fibrotic pink stroma (Fig. 7-79)
<b>Granular Cell Tumor</b>	<b>PEH</b> + pink cells in dermis w/ <b>granular cytoplasm</b> and round <b>pustulovoid bodies of Milian</b>
<b>Myofibroma/myopericytoma</b>	Dermal-SQ tumor w/ multiple <b>blue-gray (cartilage-colored) hypocellular nodules</b> surrounded by hypercellular areas containing "HPC-like" "staghorn" vessels (Fig. 7-80)
<b>Nevus Sebaceus</b>	<b>Papillomatosis</b> overlying increased number of <b>sebaceous glands directly opening</b> onto epidermis; terminal hairs replaced by <b>apocrine glands</b>
<b>Nodular Fasciitis</b>	<b>Circumscribed</b> nodule located in <b>deep dermis/SQ</b> ; stellate myofibroblasts w/ "tissue culture" appearance set in <b>loose myxoid stroma</b> with foci of <b>hemorrhage and inflammation</b>
<b>Ochronosis</b>	Yellow-brown "bananas" in superficial dermis
<b>Pseudoxanthoma Elasticum</b>	Fragmented purple elastic fibers in dermis (VVG+ and Von Kossa+)
<b>Sweet's Syndrome</b>	Dense neutrophilic infiltrate with karyorrhexis in dermis and marked papillary dermal edema; bug stains MUST be negative!
<b>Verruciform Xanthoma</b>	Verrucous hyperplasia with <b>xanthoma cells stuffed in dermal papillae</b> and superficial-mid dermis (Fig. 7-81)





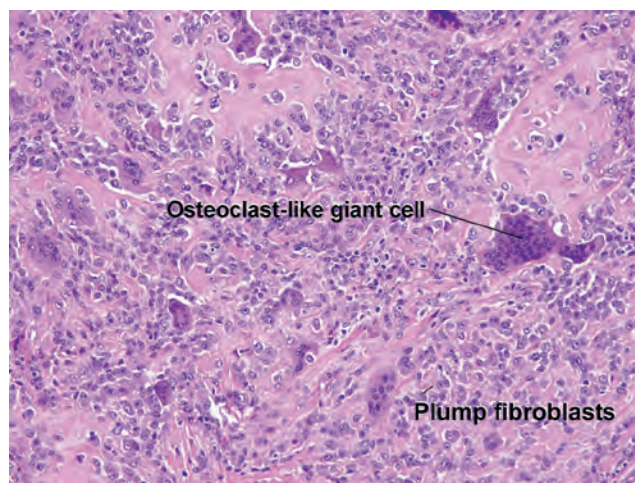
**Figure 7-78.** Endometriosis of the umbilicus. Glands and stroma are set in fibrous tissue. The glands are functional with some luminal hemorrhage. (From Weedon D. *Weedon's Skin Pathology*, 3rd Ed. Elsevier. 2009)



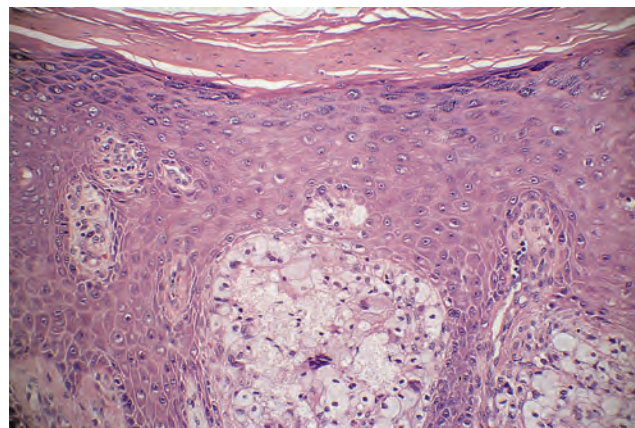
**Figure 7-80.** Myofibroma. Biphasic tumor composed of basophilic myoid nodules surrounded by immature mesenchymal cells and hemangiopericytoma-like vascular spaces. (From Busam KJ. *Dermatopathology: A Volume in the Series: Foundations in Diagnostic Pathology*, 2nd Ed. Elsevier. 2015)

## FURTHER READING

Bolognia JL, Jorizzo JL, Schaffer JV. *Dermatology*. 3rd ed. Elsevier Saunders; 2012.



**Figure 7-79.** Giant cell tumor of tendon sheath. (From Elston D, et al. *Dermatopathology*, 2nd Ed. Elsevier. 2013)



**Figure 7-81.** Verruciform xanthoma. The foam cells show some nuclear variability. (From Weedon D. *Weedon's Skin Pathology*, 3rd Ed. Elsevier. 2009)

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# Dermatologic Surgery

*Daniel B. Eisen*

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## 8.1 SURGICAL ANATOMY

- Skin lines
  - **Langer's lines:** lines along skin that will gape when punctured with a spike; lines run parallel to underlying muscles
    - Different than relaxed skin tension lines (frequently perpendicular to them, in fact)
  - **Relaxed skin tension lines** (Kraissl and Borges lines): lines that run perpendicular to underlying muscles; most elective incisions should be made **parallel** to these lines
- Head and neck anatomy
  - Arterial supply
    - Face receives blood from both the internal and external carotid systems:
      - ◆ External carotid: supplies **mid and lower face**; most important branches include:
        - ➔ **Superficial temporal artery:** supplies temple, scalp, and lateral forehead
        - ➔ **Maxillary artery:** gives rise to both the **infraorbital** and **mental** arteries, which supply the mid face, nasal dorsum, lower lip, and chin
          - ◇ Infraorbital artery anastomoses with the internal carotid-derived arteries (supratrochlear and supraorbital arteries)
        - ➔ **Facial artery:** gives rise to both the **superior** and **inferior labial** arteries, which supply the upper and lower lips, chin, nasal ala, and columella
          - ◇ Facial artery continues medially deep to the melolabial fold, where it gives rise to the **angular artery** near the base of the ala  
➔ this area is **susceptible to intraarterial injection** during filler injection!
          - ◇ Facial artery (angular artery specifically) eventually ends in anastomoses with branches of the internal carotid (**dorsal nasal artery** specifically) near the medial canthus
  - ◆ Internal carotid: supplies **mid forehead** and anastomoses with branches of the external carotid in the area of the medial canthus and dorsal nose
    - ➔ **Ophthalmic artery:** responsible for most of the facial arteries supplied by the internal carotid. It travels through the optic canal into the orbit where it supplies the **retinal**, **supraorbital** and **supratrochlear** (axial artery required for paramedian forehead flap), **infrotrochlear**, **dorsal nasal** (anastomoses with angular artery), **external nasal**, anterior and posterior ethmoidal, and lacrimal branches. These branches supply the retina, forehead, upper dorsal nose, and eyelids.
      - ◇ Branches of the ophthalmic artery anastomose heavily with those supplied by the external carotid system



- ◇ These anastomoses are important when **inadvertent intraarterial** injection of steroids or fillers occurs. **Glabellar area** is at highest risk, because of the underlying supratrochlear artery and its anastomoses → may lead to skin necrosis or **blindness** (from communication with **retinal artery**)
- **Venous system**
  - Veins typically follow their associated arteries
  - **Supratrochlear** and **supraorbital veins** drain through the orbit and into the **cavernous sinus**
    - ◆ **Danger triangle:** area extending from the two corners of the mouth to nasal bridge; infections in this area can cause **cavernous sinus thrombosis, meningitis, and brain abscesses**
- **Lymphatic system**
  - Mostly important for detection of stage 3 skin cancer metastases originating from head/neck
    - ◆ Forehead, lateral temporal, frontal, and periocular areas drain into to the **upper jugular nodes**
    - ◆ Medial midface drains into the **submandibular nodes**
    - ◆ Lower face drains into the **submental nodes**
- **Superficial musculoaponeurotic system (SMAS)**
  - Composed of muscles and fascia of the face and neck; allows for distributed force of muscles in facial expression and helps contain infection to superficial areas
  - **Motor nerves all run deep to SMAS** → staying above SMAS during facial surgery prevents motor nerve damage
  - **Sensory nerves are located superficial to SMAS** → often transected during facial surgery → numbness
- **Sensory nerves** (Tables 8-1, 8-2, Figs. 8-1, 8-2, 8-3, and 8-4)
  - Sensory innervation of face is almost entirely supplied by branches of the CN V (**trigeminal nerve**)
  - **Boards factoid:** Damage to CN V may result in trigeminal trophic syndrome and Frey's syndrome
  - **Clinical pearl:** injection of anesthetic into the supraorbital, supratrochlear, infraorbital, and mental foramina will result in prolonged anesthesia for vast majority of face (exceptions = parts of nose and angles of mouth)
- **Motor innervation** (Tables 8-3, 8-4 and Fig. 8-5)
  - Muscles of facial expression are innervated by CN VII (**facial nerve**); facial muscles

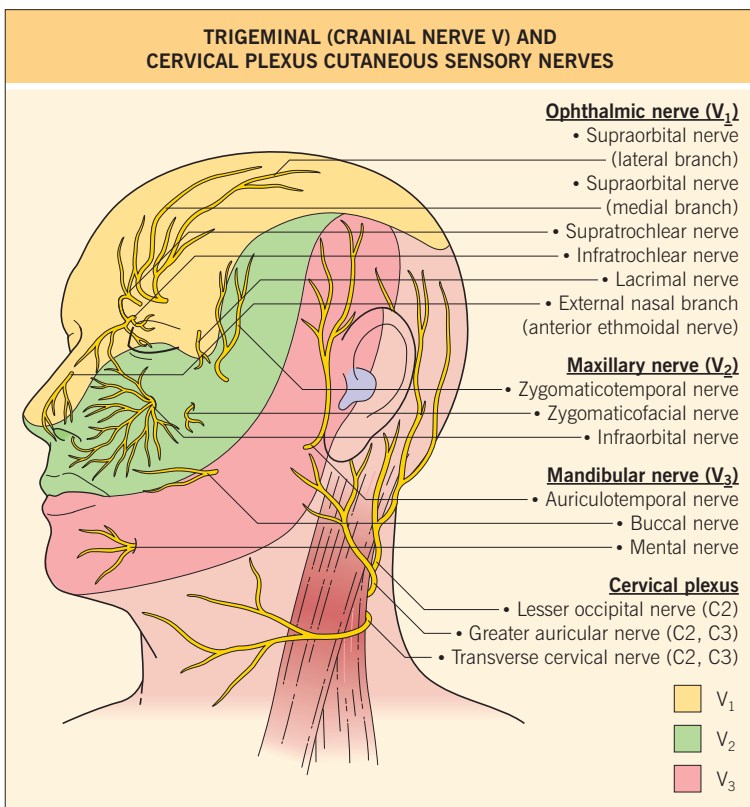
**Table 8-1.** Sensory Innervation of Head and Neck

Nerve	Innervation	Comments
<b>Trigeminal nerve</b>		
Ophthalmic (V1; has 3 major branches)	<b>Frontal nerve (two divisions)</b> Supraorbital (upper eyelid, majority of forehead, and frontal to vertex scalp) Supratrochlear (medial upper eyelid, medial forehead, and frontal scalp) <b>Nasociliary nerve (3 important divisions)</b> Infratrochlear (nasal root, medial canthus) Anterior ethmoidal ( <b>distal/inferior half of central nose:</b> dorsum, supratip, tip, and columella) Ciliary (corneal surface) <b>Lacrimal nerve (lateral eyelid, conjunctiva, and lacrimal gland)</b>	Supraorbital nerve danger zone (recently described): nerve courses superficially at vertical distances above the palpable orbital rim of 1.3 cm or greater → nerve easily injured during a deep shave, punch or ED&C of lower to midforehead → paresthesia, traumatic neuroma Supraorbital and supratrochlear nerves are commonly anesthetized via nerve block <b>Hutchinson's sign:</b> involvement of <b>nasociliary branch</b> by VZV (distal nasal vesicles, ulcers) is almost always a/w <b>herpes zoster ophthalmicus</b> ; conversely, it is very rare to have ocular involvement in absence of distal nasal skin lesions!
Maxillary (V2)	Infraorbital nerve (medial cheek, lower eyelid, <b>nasal sidewall, nasal ala, upper lip</b> , upper teeth, and maxillary gingiva) Zygomaticofacial nerve (malar eminence) Zygomaticotemporal nerve (temple and supratemporal scalp)	Infraorbital nerve is commonly anesthetized via nerve block
Mandibular (V3)	Auriculotemporal nerve ( <b>superior portion of anterior external ear</b> and auditory canal, temple, temporoparietal scalp, TMJ, outer aspect of tympanic membrane, and <b>parasympathetic innervation of parotid</b> ) Buccal nerve (buccal mucosa, angle of mouth, and gingiva) Inferior alveolar nerve (mandibular teeth) Mental nerve (chin and lower lip) Lingual nerve ( <b>somatic sensation to anterior 2/3 of tongue</b> , floor of mouth, and lower gingiva)	<b>Auriculotemporal nerve is frequently injured during TMJ surgery</b> (→ paresthesia of ear and temple) and <b>parotidectomy</b> (→ injured parasympathetic nerves erroneously reattach to sweat glands in area → <b>Frey syndrome</b> ) Mental nerve is commonly anesthetized via nerve block Mandibular nerve (V3) also provides <b>motor innervation to muscles of mastication</b> (masseter, pterygoid, temporalis, etc.)
<b>Cervical nerves</b>		
Lesser occipital (C2)	Neck, postauricular scalp	—
Greater occipital (C2)	Occipital scalp (majority)	—
Great auricular (C2, C3)	Lateral neck, angle of jaw, <b>majority of external ear</b> (both anterior and posterior portions, including earlobe), and postauricular scalp	—
Transverse cervical (C2, C3)	Anterior neck	—
Supraclavicular (C3, C4)	Anterior chest, shoulder	—

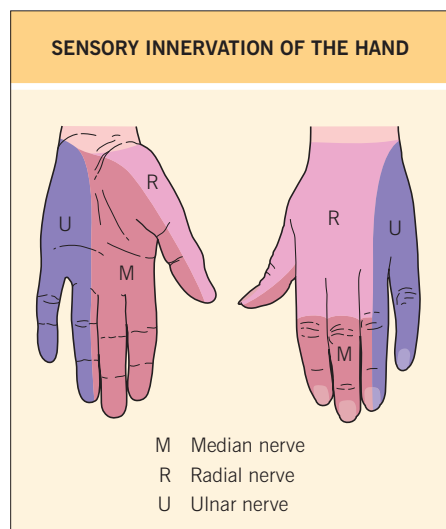
(Adapted From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 8-2.** Other High-Yield Sensory Nerve Innervation Facts

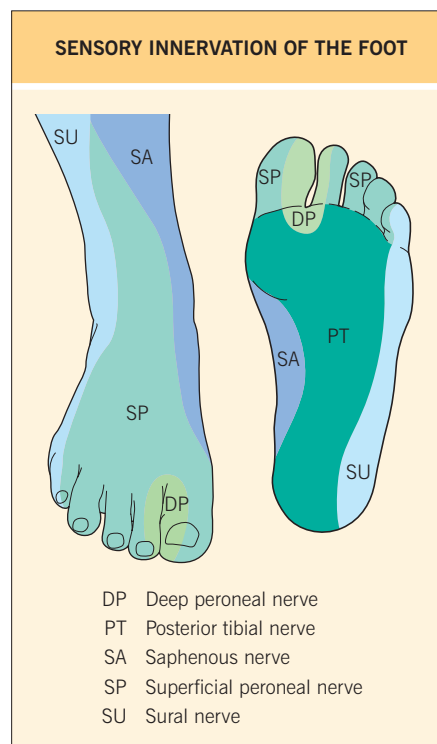
Site	Nerves and Innervation	Comments
Ear	In decreasing order of area: <b>Great auricular:</b> majority of posterior ear, and 3/4 of anterior ear (all except the quadrant innervated by auriculotemporal, and the area innervated by cranial nerves) <b>Auriculotemporal:</b> entire “anterior-superior quadrant of ear” (excluding conchal bowl, but including EAM), and superior portion of posterior helix <b>Cranial nerves (VII, IX, X):</b> Conchal bowl and EAM (most important); also contributes to posterior notch innervation <b>Lesser occipital:</b> posterior notch	<b>Ring block around ear anesthetizes everything except conchal bowl and EAM</b>
Hand	Median, radial, and ulnar	Opposing the thumb and fifth finger makes the palmaris longus tendon apparent; typically use 3–5 mL of anesthetic <b>Median nerve block:</b> inject at proximal wrist crease, between palmaris longus and flexor carpi radialis tendons (i.e., inject on the <b>radial to palmaris longus</b> , at the proximal wrist crease) <b>Ulnar nerve block:</b> inject immediately <b>radial to flexor carpi ulnaris</b> at proximal wrist crease Radial nerve block: inject along the proximal wrist crease, starting immediately lateral to radial artery, extending all the way to dorsal midwrist
Foot	Posterior tibial, saphenous, sural, superficial peroneal, and deep peroneal	Sites for foot block are highly testable! Posterior tibial nerve: inject in groove <b>between medial malleolus and Achilles tendon</b> ; is posterior to posterior tibial artery Sural nerve: inject in groove <b>between lateral malleolus and Achilles tendon</b> Deep peroneal: inject lateral to hallucis longus tendon (down to bone); may also inject SQ between second and first toe Saphenous and superficial peroneal: inject on dorsal foot, subcutaneously, <b>from malleolus to malleolus</b>
Fingers, toes	Two dorsal and two ventral nerves per digit	Multiple ways to perform digital block Classic technique: inject immediately distal MCP/MTP, using <b>1–2 mL</b> on each side (2–4 mL total per digit); <b>do NOT exceed 8 mL per digit</b> (risk of tourniquet effect) Safe to use lidocaine with epinephrine, unless patient has underlying vasoocclusive disease
Tongue	<b>Taste: CN VII</b> (chorda tympani branch; anterior 2/3) <b>Somatic sensory: trigeminal V3</b> (lingual nerve; anterior 2/3) <b>Glossopharyngeal</b> (CN IX) provides both taste and somatic sensation to <b>posterior 1/3</b> of tongue	Motor innervation of tongue: predominantly CN XII (hypoglossal nerve)
Penis	Dorsal nerve of penis bifurcates into major anterior (dorsal) and minor posterior (ventral) branches at the base of the penis → these branches supply almost all of penis	Injecting a ring of lidocaine around the base of penis anesthetizes all of penis, except periurethral glans



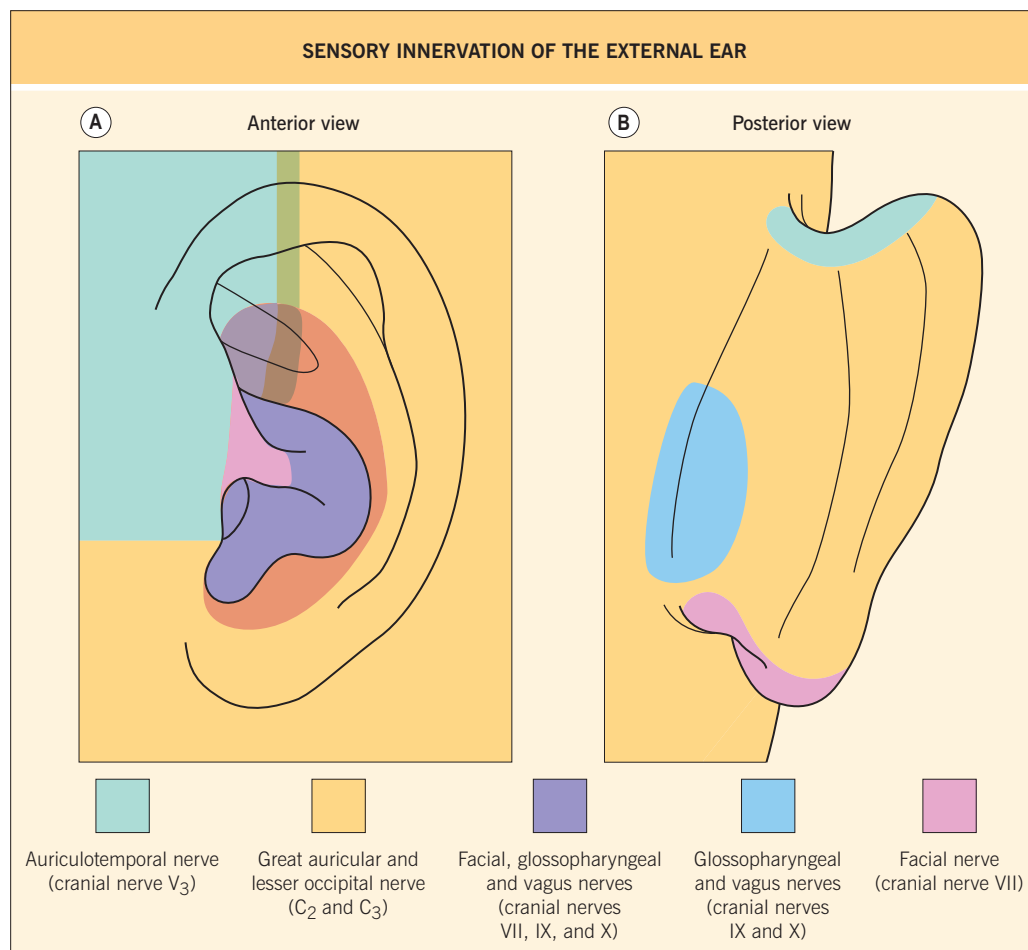
**Figure 8-1.** Trigeminal (cranial nerve V) and cervical plexus cutaneous sensory nerves. The concha and external auditory canal are variably innervated by branches of the vagus, glossopharyngeal, and facial nerves. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 8-2.** Sensory innervation of the palmar and dorsal surface of the right hand. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 8-3.** Sensory innervation of the dorsal and plantar surface of the right foot. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 8-4.** Sensory innervation of the external ear. (A) Anterolateral view. (B) Posterior view. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 8-3.** Motor Innervation of the Head and Neck

Facial Nerve (CN VII) Branch	Muscles Innervated and Normal Function	Nerve Injury-Related Findings	Other Comments
Temporal	<b>Frontalis</b> (eyebrow elevation) <b>Corrugator supercilii</b> (pulls eyebrows inferomedially) Upper portion of orbicularis oculi (tight closure of eyelids, blinking)	<b>Inability to elevate eyebrows</b> → eyebrow ptosis	<u>Targets for Botox:</u> Frontalis (horizontal forehead wrinkles) Orbicularis ("crow's feet") Corrugator supercilii (vertical glabellar lines, scowling appearance)
Zygomatic	<b>Orbicularis oculi</b> (lower portion) <b>Nasalis, alar portion</b> (flares nostrils) <b>Procerus</b> (foreshortening of nose, "horizontal glabellar lines") <u>Upper lip muscle(s):</u> Zygomaticus major (mouth angle retractor/elevator, main muscle responsible for smiling)	<b>Inability to tightly shut eyes</b> (+/- lower lid ectropion), <b>flare nostrils, and elevate upper lip</b>	<u>Targets for Botox:</u> Procerus ("horizontal glabellar lines") Nasalis, alar portion (flared nostrils)
Buccal	<b>Buccinator</b> (important muscle of mastication, works with orbicularis oris to keep cheeks pressed tightly against teeth → prevents food accumulation; also allows for high-pressure blowing) Depressor septi nasi (pulls columella toward lip) <b>Nasalis, transverse portion</b> ("bunny lines") <u>Upper lip muscles:</u> Orbicularis oris (pursing/puckering of lips, apposition of corners of mouth, pulls the lips tight up against teeth, and is required for clear speech) Zygomaticus major and minor (mouth angle retractors/elevators, main muscles responsible for smiling!) Risorius (mouth angle retractor/elevator, a lesser role in smiling) Levator anguli oris (mouth angle retractor/elevator) Levator labii superioris (elevates and everts upper lip, responsible for "gummy smile") Levator labii superioris alaeque nasi (flares nostril and elevates upper lip) <u>Lower lip muscle(s):</u> Orbicularis oris	<b>Food accumulation</b> between cheek and teeth <b>Uneven facial expression at rest and with smiling</b> (vs only upon smiling with marginal mandibular) <b>Inability to pucker/purse lips</b> Drooling as a result of ↓lip sealing ability <b>Speech is muffled</b> , cannot enunciate letters M, V, F, P, and O ↓ability to wrinkle nose (↓bunny lines)	Damage to the buccal branch of CN VII is the most likely to cause eating problems (food accumulation + drooling) and muffled speech <u>Targets for Botox:</u> Levator labii superioris ("gummy smile") Nasalis, transverse portion ("bunny lines")
Marginal mandibular	<u>Lower lip muscles:</u> Orbicularis oris Depressor anguli oris (lip depressor/retractor) Depressor labii inferioris (lip depressor/retractor) Mentalis (lower lip protrusion, chin elevator) Platysma, upper portion (intercalates with lip depressors/retractors)	Face appears normal at rest but <b>asymmetric when smiling</b> Drooling <b>Inability to evert lower lip</b>	Marginal mandibular is at <b>highest risk of causing permanent motor deficits</b> because has only 1–2 rami (in contrast to multiple rami for zygomatic and buccal branches) and is covered by thin skin and thin platysma
Cervical	<b>Platysma</b> (depresses lower jaw, tenses neck skin)	↓ability to depress lower jaw to express melancholy (" <b>grimacing</b> ")	Botox can be used to target platysma ("platysmal bands")

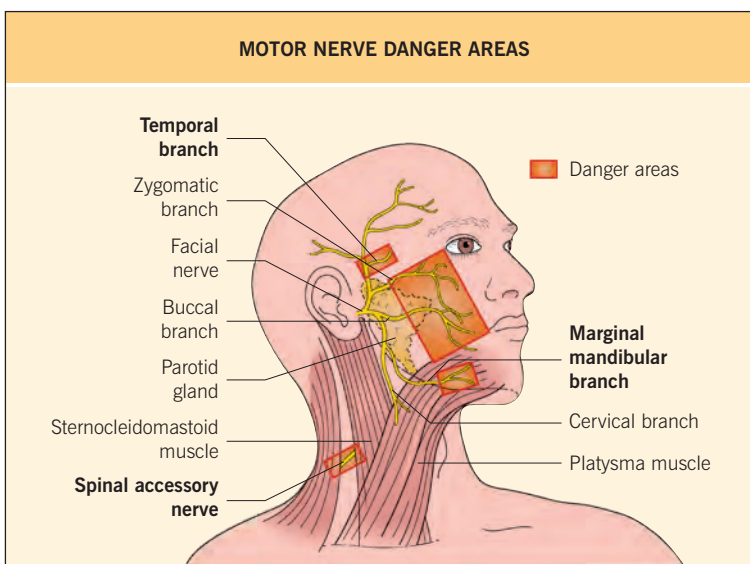
(Adapted From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)**Figure 8-5.** Motor nerve danger areas. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



Table 8-4. Cutaneous Danger Zones

Target Structure	Danger Zone	Associated Adverse Event	Other Comments
<b>Vascular occlusion from filler/steroid injections</b>			
Labial/angular artery	Near base of ala	Skin necrosis	Rx: nitroglycerin paste, LMWH, and hyaluronidase (if HA filler)
Supratrochlear artery	Glabella region	Skin necrosis, <b>blindness</b>	Same as above
<b>Motor nerve injury</b>			
Temporal nerve	Most susceptible to injury as it crosses <b>over the zygomatic arch</b>	Unilateral <b>frontalis paralysis</b> , <b>eyelid ptosis</b>	Temporal nerve runs a diagonal course from 0.5 cm below the tragus to 1.5 cm above the lateral brow; nerve is superficially located within the fascia as it crosses the zygomatic arch
Zygomatic nerve (less common)	Malar cheek	Inability to completely close eyes → corneal desiccation	Main trunks of zygomatic and buccal branches of facial nerve lie fairly deep → less commonly injured than temporal and marginal mandibular
Marginal mandibular nerve	Most susceptible 2–3 cm inferolateral to oral commissure, as it passes over the mandible	<b>Facial asymmetry upon smiling</b> (normal at rest), and inability to protrude lower lip, drooling	
Spinal accessory nerve (cranial nerve XI)	Most susceptible to injury at <b>Erb's point</b> = site where cervical plexus emerges; located along posterior border of SCM)	<b>Winged scapula, inability to abduct arm</b> , and shoulder pain	Erb's point localization: 6 cm inferior to the midpoint of an imaginary line drawn between the mastoid process and angle of jaw Great auricular and lesser occipital nerves also arise from Erb's point
Ulnar nerve	Susceptible to injury around medial epicondyle of humerus	"Claw-hand" deformity; weakness in wrist flexion, loss of flexion of fourth and fifth digits, and loss of sensation in ulnar distribution	—
<b>Other</b>			
Parotid duct	A line drawn from tragus to mid portion of the upper lip approximates its course; duct courses over masseter, pierces buccinator, and drains into the mouth at second upper molar	Parotid duct injury → sialocele (distinguished from a seroma by ↑↑amylase levels)	Rx: repair via microsurgery

(Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)

receive motor innervation from their **underside**

- ◆ Boards Factoid: as a minor function, CN VII also provides sensory input for **anterior tongue** (via chorda tympani branch) and a small amount of the **external auditory meatus**
- Facial nerve emerges from the stylomastoid foramen; the nerve **travels within the parotid gland** and then splits into 5 branches: **temporal, zygomatic, buccal, mandibular, and cervical** branches ("To Zanzibar By Motor Car")

## 8.2 SURGICAL INSTRUMENTS AND NEEDLES

- Scalpel handles
  - Bard-Parker standard handle (most common): flat; holds common blades such as the #15, #11, and #10
  - Beaver handle: round or hexagonal; holds smaller, sharper blades; useful for confined spaces or delicate tissue
- Scissors
  - Basics
    - **Short-handled** scissors useful for **delicate work**
    - Long-handled scissors extend the surgeons reach and are useful for undermining
  - Curved blades useful for undermining cysts
  - Straight blades useful for trimming tissue and cutting sutures
  - **Serrated** blades **grab tissue** better
  - Sharp-tipped scissors puncture tissue easily and are best for dissection
  - Blunt-tipped scissors are best for delicate undermining
- Scissor types
  - **Iris scissors**: sharp-tipped and short-handled; blades may be straight or curved; best for sharp dissection
  - **Gradle scissors**: similar to iris but blades curved and tapered to a fine point at tip; best for dissection of delicate tissue such as **periorbital skin**
  - **Westcott scissors**: **spring-loaded** instrument similar in appearance to Castro-Viejo; good for delicate **eyelid** dissection
  - **Mayo scissors**: characterized by its ~1 : 1 **handle-to-blade ratio**; primary purpose is coarse dissection
  - **Metzenbaum scissor**: long handles with blunt tips → useful for blunt dissection in **areas that require long reach**
  - **Supercut scissors**: one blade has a **razor edge**; "supercut" blades are available on most scissor types listed above and often are denoted with **black handles**

- Needle drivers
  - Basics
    - Smaller needle drivers with smooth jaws
      - ◆ Ideal for small, delicate needles
      - ◆ **Advantages:** smooth jaws have ↓**risk of tearing small sutures** (6-0 and smaller) and are **less damaging to fine needles** (P-3 and smaller)
      - ◆ **Disadvantages:** needles not grasped as tightly as with serrated needle drivers → ↑**needle twisting**
      - ◆ **Caution:** larger needles will ruin small needle drivers
    - Larger, serrated jaws
      - ◆ Ideal for larger needles and work on trunk
      - ◆ **Advantages:** serrated jaws hold needles more securely (prevents twisting)
      - ◆ **Disadvantage:** damages delicate needles, shreds small sutures
- Forceps
  - Basics
    - Serrated forceps: **easier to grab needle**, but results in ↑**tissue crush injury**
    - Toothed forceps: harder to grasp needle, but handles tissue gently (↓**crush injury**)
    - Combination forceps: have both teeth as well as serrated platforms → allows for gentle tissue handling and easier grasping of needle
  - Types
    - **Adson:** relatively large forceps; useful for **trunk and extremities**
    - **Bishop-Harmon forceps:** small, fine-tipped instruments; most useful for delicate tissues such as the **eyelids**; always have **3 holes** in handles to make them lighter in weight and easier to grip
    - **Jeweler's forceps:** have very pointy ends; most useful for suture removal
- Other instruments
  - Hemostats: used to grasp bleeding vessels before ligation
  - Skin hooks: available in many forms;
    - "Skin rake": a skin hook with multiple hooks
    - Hooks are the **least traumatic** way to handle tissue (during electrosurgery and suturing), but are a sharps hazard
  - Periosteal elevator: used to remove periosteum or separate nail plate from nail bed
  - Chalazion clamp: useful for eyelid surgery or on the lip to stop bleeding needles
- Surgical needles
  - Needle is composed of three parts:
    - **Shank (swage):** swaged portion that attaches to suture; **weakest** part of needle → do NOT grasp here, it will bend or break the needle
      - ◆ Size of suture track is determined by shank size, not suture size
    - **Body:** middle part; **strongest** portion of needle → always grasp here with needle driver; comes in various curvatures (most common is 3/8 circle)
    - **Tip:** sharp tip that may be round (tapered) or cutting; minimize grasping of tip → contact w/ other instruments quickly dulls the tip

- Three types of needle tips:
  - **Round (tapered):** only the tip pierces tissue (no sharp edges along arc of needle); is **less likely than cutting needles to tear tissues**; used for deep soft tissues (fat and muscle); difficult to pass through skin
  - **Cutting:** triangular-shaped needle point; preferred for skin because it easily passes through tissue; two types:
    - ◆ **Conventional cutting:** cutting surface is on **inner** portion of needle arc; ↑**risk of sutures tearing through wound edge** (this is because the cutting edge of needle faces toward the wound edge)
    - ◆ **Reverse cutting:** cutting surface is on **outer** portion of needle arc; ↓**risk of sutures tearing through wound edge**

For a more detailed discussion on surgical tools, please read: Weber LA. The surgical tray. Dermatol Clin. 1998 Jan;16(1): 17–24. PMID: 9460575.

## 8.3 SUTURE TECHNIQUES

- Knots
  - Surgeon's knot: most commonly used; essentially a square knot; first knot is double thrown to prevent slippage
  - Aberdeen hitch knot: used to tie the end of a running subcutaneous suture; is **more compact, more secure, and uses less material** than surgeon's knot
- Cuticular/epidermal suturing
  - Simple interrupted: used for wounds under **moderate to high tension**; directing the needle away from the wound results in ↑**eversion** and less frequent sunken scars
  - Simple running: used for wounds under minimal tension; **faster** to place than interrupted sutures; ↑**risk of wound dehiscence**
  - Running locked sutures: provides **hemostasis**, but has risk of strangulation
  - Vertical mattress: **strongly everts** (Vertical = eVert) wound edges, eliminates dead space, and decreases wound edge tension
  - Horizontal mattress: provides **hemostasis** (Horizontal = Hemostasis), eliminates dead space, and decreases wound edge tension; significant **strangulation risk** → do not use in poorly vascularized areas
  - Pulley suture: modified vertical mattress suture; used for wounds under high tension
  - Running horizontal mattress: same benefits as simple horizontal mattress, but is faster, provides ↑**eversion**, and ↓**strangulation risk**; improved outcomes relative to simple running sutures, but takes longer
  - Tip stitch: best stitch for **flap and M-plasty tips**; is a half-buried horizontal mattress suture
  - High-low (step-off stitch): used to correct imprecise dermal/subcuticular suturing, where one side of the wound edge is higher than the other ("step-off")

- **Subcuticular/dermal suturing**
  - Simple buried suture: traditional intradermal suture; results in minimal wound eversion and high rate of spitting sutures
  - Buried vertical mattress: has one exit point in the subcutaneous plane; **everts** tissue more than a simple buried suture
  - Set-back suture ("buried butterfly"): suture entry and exit points are both underneath the undermined wound surface; **everts tissue maximally**; results in **↓spitting sutures** and **↑cosmetic outcomes** than the buried vertical mattress technique
  - Running subcuticular: running sutures in superficial dermis, instead of along epidermal surface; primary advantage = **lack of track marks**; however, **↑rate of spitting sutures**; typically used in combination w/ buried vertical mattress sutures
  - Purse-string: traditionally used to **↓wound size** and **↓healing time**, relative to second intention; a recent RCT study did not demonstrate any difference in cosmetic appearance or scar size, but there was a trend toward faster healing time
  - Pulley suture: buried (subcuticular) pulley suture is essentially just a series of two or more simple buried subcuticular sutures; primary advantage = **permits wound closure under high tension**; disadvantage = **tissue strangulation**
  - "Figure of 8": main suturing method used to **tie off bleeding vessels**
- Suture removal recommendations (largely anecdotal): head/neck ≤7 days, extremities/torso = 10 to 14 days; the longer the sutures remain in place → **↓likelihood of dehiscence**, but **↑cutaneous track-marks**
- Suspension sutures: anchor the overlying tissue to periosteum → **removes tension from leading edge of flaps**; **prevents distortion of a free margin** (especially eyelid), also **prevents flap "tenting"** across a concavity

## 8.4 WOUND CLOSURE MATERIALS

- Suture types and properties (Tables 8-5 through 8-9)
- Suture coatings
  - Friction coatings: some multifilament sutures are coated with material to **↓friction** → more easily pulls through tissue
  - Antibiotic coatings: many sutures now contain antibiotics, chiefly **triclosan**; a recent meta-analysis demonstrated **↓surgery site infections** relative to noncoated sutures
- Barbed sutures
  - New, knot-less suturing method that is gaining popularity; barbs hold tissue in place; main benefits: **tension is distributed evenly** along entire course of wound, **faster** to use than traditional sutures; most common use = large wounds under **↑tension**
- Tissue adhesives
  - Two categories:
    - **Octyl**: octyl cyanoacrylate (Dermabond™)
    - **Butyl**: butyl cyanoacrylate (Liquiband™) and N-butyl 2-cyanoacrylate (GluSeal™)
  - ◆ Details:
    - Butyl types of cyanoacrylate dry faster than octyl type (30 vs 150 seconds); however, **butyl types are more rigid**
    - All are typically used in combination w/ traditional subcuticular sutures
    - **↑wound dehiscence rate** and unable to achieve as much eversion (vs sutures)
- Adhesive strips
  - Applied in combination with subcuticular sutures, often with the use of a topical skin adhesive (Mastisol™)
  - Studies demonstrate similar cosmetic outcomes for the combination of subcuticular sutures + adhesive strips, versus a standard bilayered suture closure

Table 8-5. Suture Types

Term	Definition	Comments
<b>Suture type (absorbable vs nonabsorbable)</b>		
Absorbable sutures	Lose most of their tensile strength within 60 days Natural fibers: digested by proteolysis Synthetic fibers: broken down by hydrolysis	Most commonly used as "deep" sutures Rate of loss of tensile strength is different than rate of suture absorption!!! Tensile strength is lost long before suture is fully absorbed ↑absorption rate in moist areas, febrile or protein-deficient patients
Nonabsorbable sutures	Maintains tensile strength for >60 days	Most commonly used as superficial/epidermal sutures
<b>Suture material (absorbable; natural vs synthetic)</b>		
Natural	Derived from natural proteins (gut, silk)	<b>Degraded by proteolysis</b> ↑inflammatory reaction and are rapidly degraded
Synthetic	Synthetic copolymers	<b>Degraded by hydrolysis</b> ↓inflammatory reaction and are slowly degraded
<b>Configuration (monofilament vs multifilament [braided])</b>		
Monofilament	Comprised of a single filament	Advantages: slide easily through tissue (because of ↓COF), harbors less bacteria than braided sutures (because of ↓capillarity), and low-minimal inflammatory reaction Disadvantages: ↓knot security (because of ↑memory and ↓COF); poor "ease of handling" (because of ↓pliability and ↑memory)
Multifilament (braided)	Comprised of multiple small filaments braided together	Advantages: ↑ease of handling (because of ↑pliability and ↓memory), ↑strength, and ↑knot security (because of ↑COF and ↓memory) Disadvantages: <b>↑bacterial infections</b> (because of ↑capillarity), and ↑inflammatory reaction

**Table 8-6.** Specific Suture Properties

Term	Definition	Comments
Ease of handling	Ease with which suture is used; <b>inversely related to memory; directly related to pliability</b>	Multifilament sutures generally have ↑ease of handling relative to monofilament
Capillarity	Ability of suture to absorb/transfer fluid	↑capillarity → suture wicks more fluid from wound surface into wound (conduit for bacteria) <b>Multifilament sutures have ↑capillarity → ↑infection</b>
Size (USP size)	Diameter of suture material required to achieve a given tensile strength	<b>More zeroes = smaller suture</b> diameter (6–0 suture is smaller than 5–0) Inherent strength of the material also affects USP size (Prolene is inherently stronger than gut → 4–0 Prolene will be smaller in diameter than 4–0 gut)
Tensile strength	Force required to snap the suture	<b>Synthetic sutures are generally stronger</b> than natural materials A suture that has been knotted only has 1/3 of its original tensile strength
Coefficient of friction (COF)	Degree of friction encountered when you try to pull suture through tissue	<b>↓COF → ↓knot stability</b> (slippery) Polypropylene (Prolene) has a very low COF → easily slides through tissue → ideal for subcuticular sutures, but requires more throws to secure knot Braided sutures have ↑COF → ↑knot stability
Pliability	Ease with which suture can be bent into a knot; felt as “stiffness” of suture	<b>Braided sutures have ↑pliability → easier to tie knots/↑ease of handling</b> Pliability and memory are the two main determinants of “ease of handling”
Memory	Tendency of suture to retain its original configuration; <b>determined by elasticity, plasticity, and suture diameter</b>	Is one of two main determinants of knot security (other is COF) Is one of two main determinants of “ease of handling” (other is pliability) <b>↑memory → ↓knot security and ↓ease of handling</b> Monofilament sutures have ↑memory relative to braided sutures
Plasticity	Ability of suture to retain its tensile strength after being stretched into a new shape	↑plasticity allows suture to <b>stretch to accommodate postoperative swelling</b> without cutting into tissue (Prolene has ↑plasticity than nylon)
Elasticity	Ability of a suture to return to its original length after being stretched	↑elasticity is an <b>ideal suture property</b> : elasticity allows suture to stretch to accommodate swelling, and later, resume its original shape → keeps wound edges approximated after edema has resolved <b>Polybutester</b> (Novafil) and <b>poliglecaprone-25</b> have ↑elasticity → good for swollen tissues
Knot security	Strength of the knot	Higher with <b>multifilament</b> sutures <b>Directly proportional to COF</b> <b>Inversely related to memory</b>
Inflammatory potential/tissue reactivity	Amount of foreign body inflammation incited by suture	Much higher with <b>natural</b> sutures (gut, silk) than synthetic ones

**Table 8-7.** Most Commonly Used Absorbable Sutures

Suture	Configuration	Tensile Strength (50%)	Absorption	Ease of Handling	Knot Security	Tissue Reactivity	Comments
Fast-absorbing gut	Virtually monofilament	3–5d	21–42d	Fair	Poor	Low	Often used for skin grafts
Fast-absorbing Polyglactin 910 (Vicryl Rapide™)	Braided	5d	42d	Good	Fair	Low	—
Plain gut	Virtually monofilament	7–10d	70d	Fair	Poor	<b>Moderate-high</b>	—
Polyglecaprone-25 (Monocryl™)	Monofilament	7–10d	90–120	Good	Good	<b>Minimal</b>	↑knot security and ease of handling relative to other monofilaments; <b>least inflammatory; highest initial tensile strength</b>
Polyglycolic acid (Dexon™)	Braided	14d	90d	Good	Good	Low	—
Chromic gut	Virtually monofilament	21–28d	90d	Poor	Poor	Moderate (but less than plain gut)	Pretreated w/ chromium salts to slow degradation
Polyglactin 910 (Vicryl™)	Braided	21d	56–70d	Good	Fair	Low	↑rate of spitting sutures relative to Monocryl
Polyglyconate, a copolymer of glycolic acid and polytrimethylene carbonate (Maxon™)	Monofilament	30–40d	180d	Fair	Good	Low	Nearly equivalent to PDS in terms of durability, but has ↑knot security and is easier to handle
Polydioxanone (PDS II™)	Monofilament	<b>30–50d</b>	<b>180–240d</b>	Poor	Poor	Low	<b>Longest lasting absorbable suture</b> → good for high-tension closures

(Adapted From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Table 8-8.** Most Commonly Used Nonabsorbable Sutures

Suture	Configuration	Ease of Handling	Knot Security	Tissue Reactivity	Comments
Silk	Braided	<b>Gold standard</b>	Good	<b>High</b>	Used on mucosal surfaces Best handling of any suture <b>Second highest tissue reactivity (#1 is plain gut)</b>
Nylon (Ethilon™, Dermalon™)	Monofilament	Good to fair	Poor	Very low	Most commonly used for skin surface closure Clear nylon may be used as a permanent deep suture for periosteal tacking or to prevent scar spread
Polypropylene (Prolene™, Surgilene™)	Monofilament	Good to fair	Poor	Least	<b>Least inflammatory</b> nonabsorbable suture; has extremely low COF → ideal for <b>running subcuticular suturing</b> <b>Stretches with swelling</b> , rather than cutting into tissue
Polyester (Ethibond™, Dacron™, Mersilene™)	Braided	Very good	Good	Minimal	<b>Highest tensile strength</b> of any nonabsorbable suture (excluding stainless steel) Used on mucosal surfaces Similar to silk, but less inflammatory
Polybutester (Novafil™)	Monofilament	Good to fair	Poor	Low	Most useful for skin closure when significant edema is expected (because of ↑elasticity)

(Adapted From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 8-9.** High-Yield Suture Comparisons

Property	Absorbable (Most to Least)	Nonabsorbable (Most to Least)
Tissue reactivity	<b>Surgical gut</b> > Polyglycolic acid, polyglactin 910, and lactomer > polydioxanone > <b>polyglyconate = poliglecaprone 25</b>	<b>Silk</b> > Nylon > Polyester, polybutester > <b>polypropylene (least)</b>
Initial tensile strength	<b>Poliglecaprone 25</b> > polyglyconate > polydioxanone > polyglactin 910, lactomer > polyglycolic acid > surgical gut	<b>Stainless steel</b> (#1 overall) > <b>polyester</b> (#1 nonmetal suture) > nylon, polybutester > polypropylene > silk
Time required to decrease to 50% of initial tensile strength	(Longest time to shortest) <b>Polyglyconate = polydioxanone</b> > polyglactin 910 > polyglycolic acid = chromic gut > poliglecaprone 25 = plain gut > Vicryl™ rapide > <b>fast-absorbing gut</b>	—
Absorption time	(Longest time to shortest) <b>Polydioxanone</b> > polyglyconate > poliglecaprone 25 = polyglycolic acid > polyglactin 910 = plain gut > Vicryl™ rapide > <b>fast-absorbing gut</b>	—

- Staples
  - Traditional staples: typically used on scalp by dermatologic surgeons; advantages: **quick, easy** application, lower risk of strangulation, and ↓infection rates compared w/ sutures; disadvantages: ↑pain after closure
  - Absorbable staples: recently introduced; staples are buried similar to sutures; ↓pain, ↑cosmetic outcomes compared with traditional transcutaneous staples

## 8.5 LOCAL ANESTHETICS AND PERIOPERATIVE PAIN CONTROL

- Three major categories of afferent sensory fibers:
  - **C fibers**: small diameter, unmyelinated nociceptors; transmit **diffuse, dull, and aching** pain
  - **Aδ fibers**: medium diameter, lightly myelinated fibers; transmit **sharp, localized** pain and **temperature**
  - **Aβ fibers**: fast-conducting, large-diameter, myelinated fibers; detect **vibration and light pressure**; large Aβ fibers respond slowly to local anesthetic → patients continue to “feel something, but not pain” after injection
- Local anesthetics (Table 8-10)
  - Mechanism: reversible **inhibition of sodium ion influx** → blocks nerve conduction
  - Chemical structure
    - **Aromatic end** – lipophilic, affects **potency and duration** of action
    - **Intermediate chain** – linkage portion
      - ◆ **Amides** (most commonly used)
        - Metabolized via **CYP 3A4** system in **liver**
        - **Esters vs amides**: “two ‘I’s’ = amIde”
        - Allergic reactions are rare; typically occur as a result of **methylparaben preservative**, not anesthetic (if occurs, switch to preservative-free lidocaine)
        - Contraindications: **end-stage liver disease**
      - ◆ **Esters**
        - Metabolized via **pseudocholinesterases** in **plasma**; renally excreted
        - Less stable in solution
        - **Frequent allergic reactions** to **PABA** metabolite
          - ◇ Cross-reacts with multiple contact allergens (Mnemonic “**PPPESTAA**”): Paraphenylenediamine (PPD), PABA, Para-aminosalicylic acid, Ethylenediamine,

**Table 8-10.** Testable Facts Regarding Specific Anesthetics

Anesthetic	Pregnancy Category	Onset (min)	Duration w/o epi (min)	Duration w/ epi (min)	Max Adult Dose (mg/kg) wo/w epi	Most Important Points
<b>Amides</b>						
Lidocaine (xylocaine)	B	< 1	30–120	60–400	4.5 mg/7 mg (safe to use up to 55 mg/kg w/ tumescent anesthesia)	<b>Fastest onset</b> of action (<1 min) <b>Anesthetic of choice in pregnant women</b>
Mepivacaine (carbocaine)	C	3–20	30–120	60–400	6 mg/8 mg	Slowest onset of action Risk of fetal bradycardia
Prilocaine	B	5–6	30–120	60–400	7 mg/10 mg	<b>Risk of methemoglobinemia</b> (↑risk with G6PD deficiency and in children <1 y.o.) Component of topical EMLA
Etidocaine	B	3–5	200	240–360	4.5 mg/6.5 mg	—
Bupivacaine (Marcaine)	C	2–10	120–240	240–480	2.5 mg/3 mg	<b>Longest duration of action</b> , when combined with epinephrine (up to 8 hours) Most common use: added to lidocaine for big Mohs cases to provide long-lasting anesthesia <b>Highest risk of cardiac toxicity!</b> Risk of fetal bradycardia
Ropivacaine	B	1–15	120–360	Same as without epi	3.5 mg/NA	Longest duration of action in absence of epinephrine (up to 6 hours)
<b>Esters</b>						
Procaine (aka novocaine)	C	5	15–30	30–90	10 mg/14 mg	Shortest duration of action
Chlorprocaine	C	5–6	30–60	Not known	10 mg/NA	—
Tetracaine	C	7	120–240	240–480	2 mg/2 mg	—

(Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)

Sulfonamides, Thiazides, Anesthetics (esters), Azo dyes

→ Contraindications: allergy to PABA or cross-reacting substances, **pseudocholinesterase deficiency**, and renal insufficiency

- **Amine end** – hydrophilic, binds sodium channel, and determines **onset of action**

■ Additives to local anesthetics

- **Epinephrine** (1:200 000 equally as effective, w/ ↓toxicity than 1:100 000)
  - ◆ Mechanism: vasoconstriction → localization of anesthetic
  - ◆ Advantages: ↑**safety and duration** of anesthetic (because less diffusion and absorption), ↓**bleeding** (full vasoconstrictive effect takes 7–15 minutes)
  - ◆ Disadvantages: ↓**uterine blood flow** (pregnancy category C)
  - ◆ Contraindications: pheochromocytoma and uncontrolled hyperthyroidism
  - ◆ Caution with: pregnancy (shown to be safe if dilute epinephrine to 1:300 000), severe CV disease, HTN, glaucoma, and drugs (β-blockers, TCAs, and MAO-I)
- **Sodium bicarbonate 8.5%** (1 mL per 10 mL of 1% lidocaine)
  - ◆ Mechanism: bicarbonate raises pH to near-physiologic levels → majority of anesthetic remains neutral/uncharged → more rapidly crosses nerve membranes
  - ◆ Advantages: ↑**speed of onset** and ↓**injection pain** (as a result of physiologic pH)

- ◆ Disadvantages: ↓**shelf-life**, because of epinephrine degradation (must use within 1 week)

○ Hyaluronidase

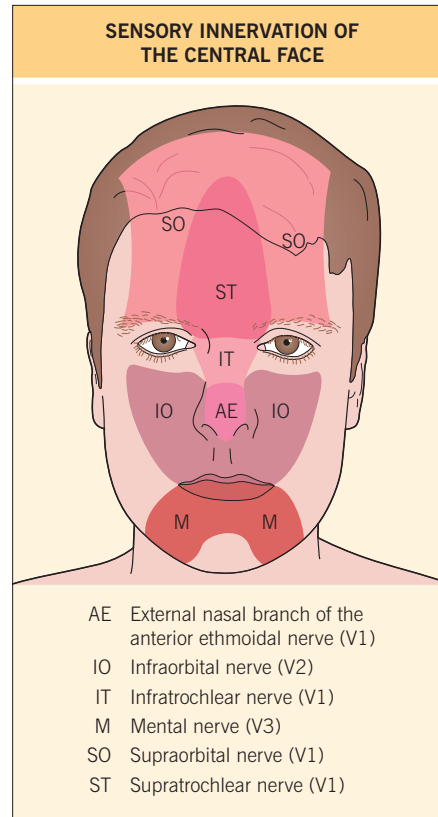
- ◆ Mechanism: digests hyaluronic acid
- ◆ Advantages: ↑anesthetic diffusion and ↓tissue distortion from fluid infiltration
- ◆ Disadvantages: ↓duration of anesthesia and ↑anesthetic toxicity (as a result of ↑absorption); also contains the contact allergen **thimerosal**

■ Lidocaine

- Most commonly used local anesthetic; anesthetic of choice for pregnant women
- Most commonly used concentrations: **1% (10 mg/mL)**, **2% (20 mg/mL)**, and **0.1% tumescent (1 mg/mL)**
- Must know the maximum doses!
  - ◆ **Without epinephrine** = **4.5–5 mg/kg** (35 mL of 1% lidocaine in 70 kg patient)
    - Pediatric = 1.2–2 mg/kg (2.4 mL of 1% lidocaine in a 20 kg patient)
  - ◆ **With epinephrine** = **7 mg/kg** (49 mL of 1% lidocaine in 70 kg patient)
    - Pediatric = 3–4.5 mg/kg (6 mL of 1% lidocaine in a 20 kg patient)
  - ◆ **Tumescent anesthesia** = **55 mg/kg**
    - 10-fold dilution of standard 1% lidocaine with 1:100 000 epinephrine (= 0.1% lidocaine with 1:1 000 000 epinephrine)
    - Advantages: ↓**bleeding**, ↑**duration** of anesthesia, and **avoids complications** a/w general surgery (↓morbidity and mortality)

- Caution w/ **end-stage liver disease** → ↑**risk of lidocaine toxicity** (metabolized by liver)
- Pregnancy class B, lactation safe
- Must know the presentations of the various adverse reactions to local anesthetics!
  - Mnemonic: lidocaine overdose stages loosely resemble alcohol overdose:
    - **Mild** (~“Happily buzzed and tingly feeling”): restlessness, euphoria, talkativeness, lightheadedness, “funny tingling” around mouth and hands, metallic taste, and **circumoral numbness**
    - **Moderate** (~“Hammered! Can’t hear or speak well”): nausea, vomiting, psychosis, **tinnitus**, muscle twitching/tremors, blurred vision, **slurred speech**, and confusion
    - **Severe** (~“Severe alcohol poisoning”): seizures and cardiopulmonary depression
    - **Life-threatening**: coma and cardiopulmonary arrest
  - Easiest way to distinguish between vasovagal (most common), epinephrine reaction, and anaphylaxis (most severe) is to **compare BP and HR** (Table 8-11)
- Injection techniques to decrease pain (examination favorite!):
  - Mildly irritate (**pinch, rub**) surrounding skin at the time of injection → decreases transmission of pain signals to brain (“**Gate theory**” of pain)
  - Use small diameter (30-gauge) needle
  - **Add bicarbonate** to anesthetic
  - **Warm anesthetic** to body temperature
  - Pretreat w/ topical anesthetics or ice packs
  - Inject slowly, starting deep in SQ → gradually move superficial
  - Reintroduce needle at previously anesthetized areas and fan out
  - Music and mental distraction also reduce the perception of pain

- **Regional blocks** (see related discussion in Surgical Anatomy section)
  - **Facial**: supraorbital, infraorbital, and mental nerves are the most important (Figs. 8-6 and 8-7)
  - **Feet**: posterior tibial, saphenous, superficial peroneal, and sural nerves (Figs. 8-8, 8-9, and 8-10)

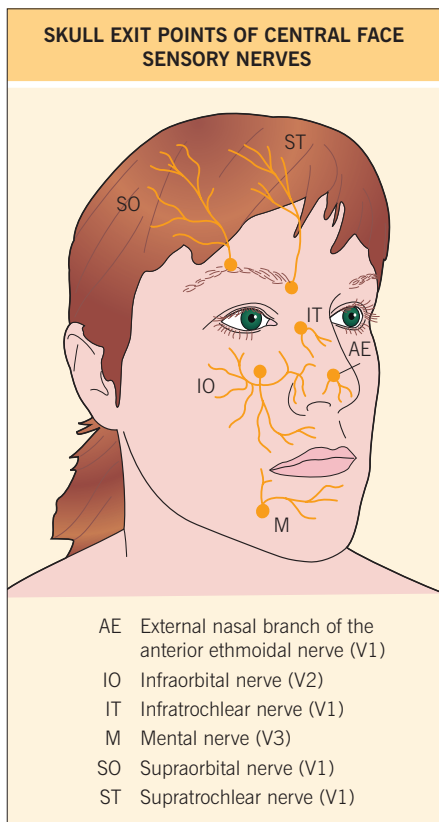


**Figure 8-6.** Sensory innervation of the central face. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

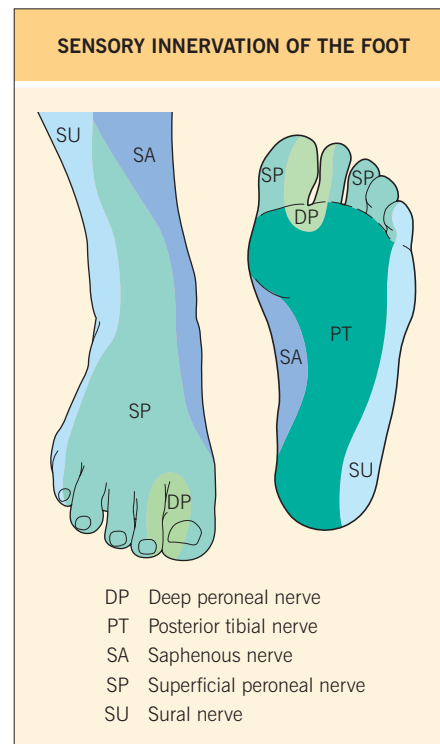
**Table 8-11.** Differential Diagnosis of Local Anesthetic Systemic Reactions

Diagnosis	Pulse Rate	Blood Pressure	Signs and Symptoms	Emergency Management
Vasovagal reaction	Low	Low	Excess parasympathetic reaction; diaphoresis, hyperventilation, and nausea	Trendelenburg, cold compress, and reassurance
Epinephrine reaction	High	High	Excess $\alpha$ - and $\beta$ -adrenergic receptor stimulation; palpitations, muscle tremors, nervousness	Reassurance (usually resolves within minutes), phentolamine, and propranolol
Anaphylactic reaction	High	Low	Peripheral vasodilation with reactive tachycardia; stridor, bronchospasm, urticaria, and angioedema	Epinephrine 1 : 1000 0.3 mL SQ injection, antihistamines, corticosteroids, fluids, oxygen, and airway maintenance
<b>Lidocaine overdose</b>				
1–6 mcg/mL	Normal	Normal	Circumoral and digital paresthesias, restlessness, metallic taste, talkativeness, euphoria, and lightheadedness	Observation
6–9 mcg/mL	Normal	Normal	Nausea, vomiting, muscle twitching, tremors, blurred vision, slurred speech, tinnitus, confusion, excitement, and psychosis	Diazepam; airway maintenance
9–12 mcg/mL	Low	Low	Seizures, cardiopulmonary depression	Respiratory support
>12 mcg/mL	None	None	Coma; cardiopulmonary arrest	Cardiopulmonary resuscitation and life support

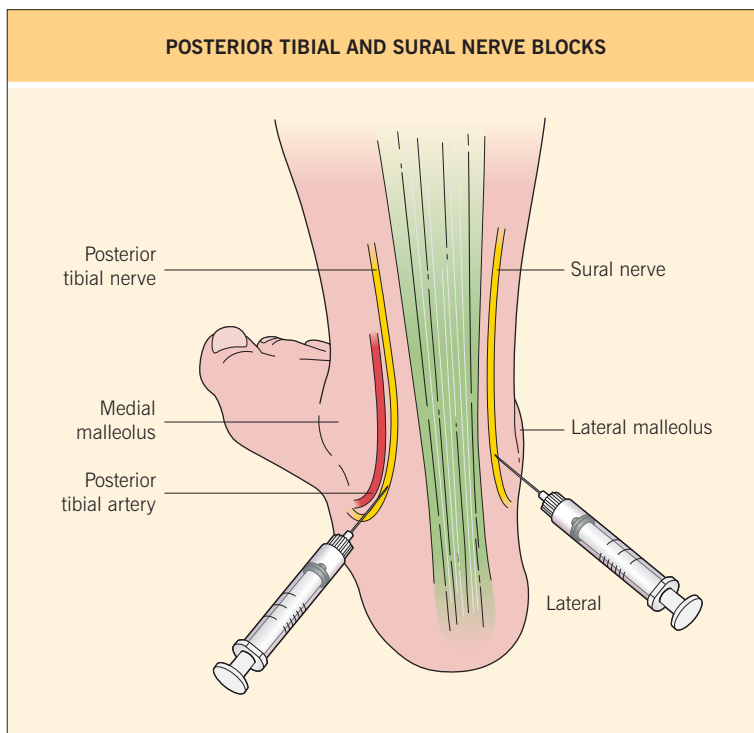
*In case of systemic reactions during or after local anesthetic injections, hemodynamic signs are helpful in determining the cause of the reaction.*



**Figure 8-7.** Skull exit points of central face sensory nerves. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

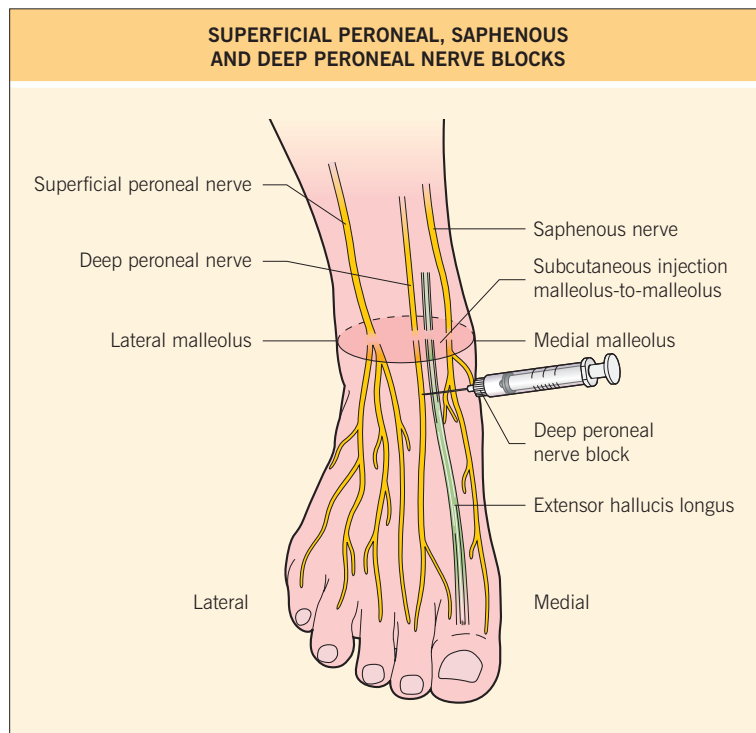


**Figure 8-8.** Sensory innervation of the dorsal and plantar surface of the right foot. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

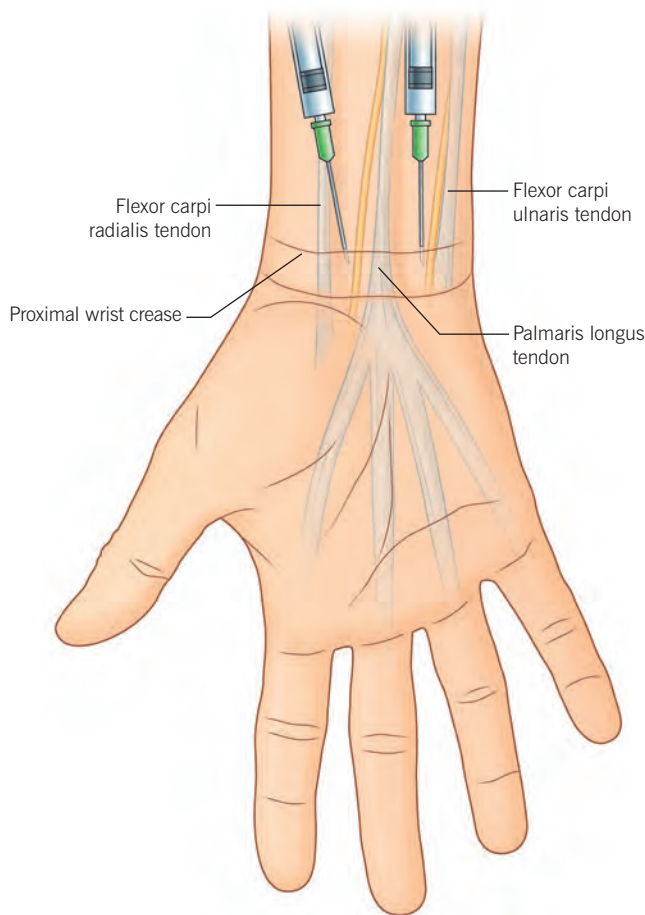


**Figure 8-9.** Posterior tibial and sural nerve blocks. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

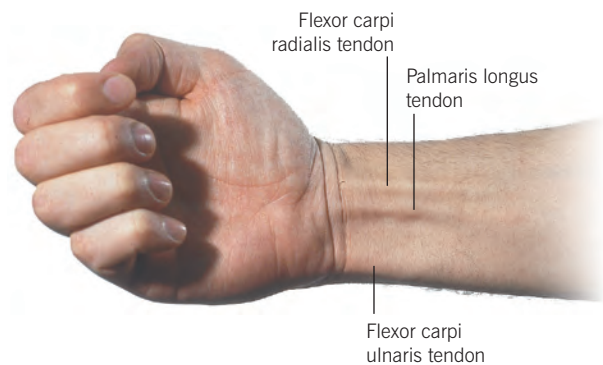




**Figure 8-10.** Superficial peroneal, saphenous, and deep peroneal nerve blocks. Great toe dorsiflexion aids in visualizing the extensor hallucis longus tendon. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

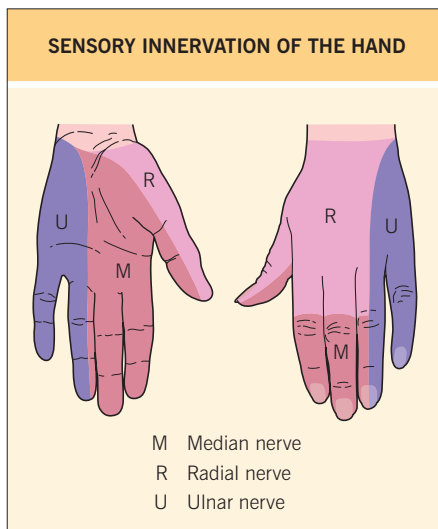


**Figure 8-11.** Landmarks for median and ulnar nerve blocks. The tendons can be easily visualized and palpated. (From Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)



**Figure 8-12.** Landmarks for median and ulnar nerve blocks. Nerve blocks are delivered by insertion of needles at the proximal crease of the wrist. (From Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)

- Fingers (digital block): two dorsal and two volar nerves run along sides of finger
- Hand: median and ulnar nerves (Figs. 8-11, 8-12, and 8-13)
- Risks of nerve blocks: nerve injury, vessel trauma, and intravascular infiltration
- Topical anesthetics
  - Stratum corneum limits efficacy of topical anesthetics on keratinized skin → mucosal sites benefit more
  - Boards fodder:
    - EMLA (Eutectic Mixture of Local Anesthesia): mixture of 2.5% lidocaine + 2.5% prilocaine; requires occlusion; risk of methemoglobinemia in infants from prilocaine; cannot use near eye (→ corneal injury); on histology, causes artifactual



**Figure 8-13.** Sensory innervation of the palmar and dorsal surface of the right hand. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

#### swelling and vacuolization of upper epidermis + basal layer split

- LMX4 (lidocaine 4%): unlike EMLA, does not require occlusion
- Cocaine: only ester anesthetic to cause **vasoconstriction** (all others → vasodilation)
- Benzocaine (Anbesol™): used on mucous membranes
- Proparacaine and tetracaine: used for ocular anesthesia
- True allergies to local anesthetic are rare!
  - More commonly, patients are sensitive to the epinephrine contained within them
  - True “allergies” are usually as a result of parabens, para-amino benzoic acid (PABA), or metabisulfide preservatives
  - **Amide anesthetics do not cross-react w/ ester anesthetics**
- Adjunctive pain/anxiety-control measures:
  - Preoperative anxiolytic
    - **Benzodiazepines** (diazepam and midazolam)
      - generally safe; can reverse overdose w/ **flumazenil**
  - Conscious sedation
    - Utilization of sedatives and dissociative medications to decrease consciousness without needing to manage the patient’s airway; requires monitoring
  - Postoperative pain management
    - **Pain is at maximal severity on night of surgery → drops dramatically each additional day after surgery**
      - ◆ Severe pain should not be experienced for >4–5 days → if so, consider drug-seeking behavior, infection, or hematoma
    - Rest, Ice, Compression, Elevation (RICE)

- NSAID + acetaminophen combination (superior to either alone)
  - ◆ Acetaminophen maximum dose/24 hours = 4 g if <60 years old or 3 g if >60 years old
  - ◆ In setting of liver failure, 2 g/24 hours of acetaminophen alone is safer than either NSAIDs or narcotic
- Opioids
  - ◆ Occasionally necessary (taut scalp/forehead closures, large trunk excisions)

## 8.6 ANTISEPSIS – GARBS AND PREPS

- Hair removal
  - **Do NOT** shave! Shaving introduces microscopic abrasions → bacterial access into wound
  - **DO** use clippers and/or chemical depilatories
- Hand hygiene
  - Skin flora is divided into two groups:
    - **Transient bacteria (bad)**: reside superficially; easy to remove w/ hand washing; responsible for most healthcare-worker-transmitted infections
    - **Resident bacteria (ok)**: reside deeper; difficult to remove; not commonly a/w nosocomial infections; examples = *S. epidermidis* and diphtheroids
  - Hand hygiene agents: **alcohol or alcohol + chlorhexidine reduces bacterial counts most**, followed by: chlorhexidine only > iodophors > triclosan > soap
- Antiseptic skin preparations
  - Activity of these agents is the same as for the hand hygiene products above.
  - Important considerations:
    - Alcohol: flammable → may lead to fires, especially in hair baring areas
    - **Chlorhexidine: should never be used around the eye (→ severe corneal damage) or ears (ototoxic).** *Serratia* may colonize chlorhexidine bottles → infection (Table 8-12)

## 8.7 ELECTRICAL HEMOSTASIS

### Introduction

- Electrocautery and electrosurgery often incorrectly used interchangeably
  - Electrosurgery: high-frequency alternating current to conduct energy via a cold-tipped electrode
    - High-frequency alternating current prevents the depolarization of muscles and nerves
    - Employs an unheated electrode and relies on the high resistance of human tissue, a poor electrical conductor, to halt the flow of current and to convert electrical energy into thermal energy, resulting in hemostasis via heat-induced tissue destruction

Table 8-12. Antiseptics

Agent	Mechanism	Onset	Advantages	Disadvantages	Residual Activity	Comments
Alcohol (isopropyl and ethanol)	Denatures cell walls; 100% alcohol is less effective than <b>70% (optimal strength)</b>	Very rapid ( <b>fastest</b> )	<b>Very broad spectrum:</b> G(+), G(-), mycobacteria, and many viruses	<b>Inactive against spores, protozoan oocysts, and certain nonenveloped viruses; not effective for soiled hands</b>	None	Flammable → caution w/ electrosurgery and lasers
Chlorhexidine (2%–4%)	Disrupts cell membranes	Rapid	<b>Broad spectrum:</b> G(+), G(-), viruses, fungi, and mycobacteria; not inactivated by organics (blood and sputum)	<b>Inactive against spores; ototoxicity, keratitis, and conjunctivitis</b>	<b>#1 overall</b> (>6 hours; remains bound to stratum corneum)	<b>Longest acting</b> <b>Often avoided around eyes/ears</b>
Chloroxylenol (parachloro-metaxylenol)	Deactivates enzymes and alters cell walls	Slow	Reasonably broad spectrum: G(+) > G(-), mycobacteria, and viruses	Not as broad spectrum, fast-acting, nor as long-lasting as chlorhexidine; ↓efficacy in presence of organics	Good	<b>Ineffective against pseudomonas</b> unless combined w/ EDTA
Hexachlorophene	Inactivates enzymes	Slow	Effective against staph	Ineffective against G(-), fungi, and mycobacteria; <b>neurotoxicity; teratogenic</b>	Modest	No longer used Highly absorbed through skin → infants bathed w/ this agent developed <b>neurotoxicity</b>
Iodine and iodophors	Oxidation → disruption of protein synthesis and cell membranes	Rapid	Very broad spectrum: G(+), G(-), <b>bacterial spores</b> , mycobacteria, viruses, and fungi	<b>Skin irritation and discoloration</b> (less w/ iodophors); <b>inactivated by blood and sputum</b>	Minimal	Must wait for it to dry to be effective
Quaternary ammonium compounds (Benzalkonium)	Induces leaks in cytoplasmic membranes	Slow	G(+) and lipophilic viruses	Ineffective against G(-), mycobacteria and fungi; <b>inactivated by organic materials and cotton gauze</b>	Good	Used in <b>eyedrops</b>
Triclosan	Alters cytoplasmic membrane and synthesis of RNA, fatty acids, and proteins	Rapid	G(+), mycobacteria, and candida; not inactivated by organic material	Ineffective against G(-) and filamentous fungi	Good	Not as effective as chlorhexidine, iodophors, or alcohol Binds <b>enoyl-acyl carrier protein reductase</b> in bacteria
Soap and water	Detergent; removes dirt and organic substances	Very rapid	Highly effective against <b>C. difficile</b> and <b>Norwalk</b> virus	Inconvenient; skin irritation	None	Most appropriate for soiled hands

- Types: electrosection, electrocoagulation, electrodesiccation, and electrofulguration
- Electrocautery: direct application of heat to tissue via a hot-tipped electrode generated by a direct current
  - There is **no current flowing** through the patient and hemostasis is achieved by the direct application of heat (vs electrosurgery where an alternating current is present)

## Monopolar vs bipolar

- These two (frequently misused) terms should NOT be used when describing electrosurgery!

## Monoterminal and biterminal devices

- Monoterminal and biterminal: refers to the **absence or presence of a grounding electrode**
- Monoterminal circuits (**electrodesiccation** and **electrofulguration**) employ an active electrode **without a grounding pad**; because there is no dispersive electrode to dissipate the accumulated current, **higher voltages** are needed to reach the desired level of effective tissue destruction; only electrical difference between electrofulguration and electrodesiccation is that the probe does not directly contact the skin in electrofulguration

**Table 8-13.** Mono- versus biterminal

Term	Definition
Monoterminal	No grounding electrode; electrons from patient disperse to table, floor, walls, and air
Biterminal	Presence of a grounding electrode (either grounding pad or biterminal forceps)

- Biterminal circuits (**electrocoagulation** and **electrosection**) always employ a **dispersive electrode** to recycle current
  - Current travels through the body from the active electrode to the dispersive electrode (**grounding pad** or **biterminal forceps**) and exits via the latter; dispersive electrodes provide an outlet of return of current to the electrosurgical device, permitting **increased amperage and reduced voltage**; only electrical difference between electrocoagulation and electrosection is the degree of damping (Table 8-13)

## Waveforms

- Waveforms are used to describe the characteristics of a wave's amplitude, frequency, and continuity (continuous waveforms result in greater heating than discontinuous ones)
- **"Undamped" waveform** (may be continuous or discontinuous): amplitude remains unchanged throughout sine wave; results in **pure cutting, no hemostasis**
  - Example: pure electrosection
- **"Damped" waveform** (may be continuous or discontinuous): amplitude decreases with time and eventually reaches zero; the more rapidly the wave's amplitude diminishes to zero, the more damped the current; increased damping results in **greater coagulation/destruction and less cutting**
  - Examples: electrodesiccation, electrofulguration, and electrocoagulation

## Electrocautery

- Electrocautery is distinguished from electrosurgery by its absence of alternating current
- **Direct current** in electrocautery supplies energy to the device's tip → generates heat → **red-hot tip** is applied directly to tissue
- Current does not pass through the patient; destruction is achieved solely by heat conducted to the tissue
- Safe in patients w/ implantable cardioverter-defibrillators (ICDs) and pacemakers because of the absence of current traveling through the body
- Additional advantages: portable and effective in a wet field

## Electrodesiccation

- **Monoterminal** device
- Causes superficial ablation when a probe is placed in direct contact w/ tissue

- When the probe directly contacts tissue, this **low-amperage high-voltage** system slowly heats tissue → results in water loss → dehydration and superficial mummification, but no significant protein denaturation

## Electrofulguration

- **Monoterminal** device (e.g., hyfrecator)
- Causes surface carbonization when electrical probe is held at a distance from tissue (**no direct contact**)
- When the probe is held at a distance, this **low-amperage high-voltage** system produces an ionized current between the probe and tissue ("**spark gap**") → superficial tissue ablation occurs, but the underlying tissue is protected from thermal heat spread by superficial carbonization
- Similar to electrodesiccation in most respects, with the exception that the spark gap and resultant superficial carbonization result in **more limited, superficial** tissue destruction

## Electrocoagulation

- Form of electrosurgery using a **biterminal** device
- **High-amperage low-voltage** form of electrosurgery; utilizes a **moderately damped waveform**
- Tissue is ablated by direct contact with probe → slow cellular heating → intracellular fluid evaporation, coagulum formation, and resultant protein denaturation
- **↑current (amperage)** penetrates **more deeply** than in electrodesiccation → ↑potential for deep tissue destruction and hemostasis

## Electrosection

- Like electrocoagulation, electrosection is a **high-amperage low-voltage** method of electrosurgery using a **biterminal device**
- In contrast to electrocoagulation, electrosection employs an **undamped waveform** for the purpose of pure cutting, as with a blade
- If used on a "blended mode" with electrocoagulation → provides a **mixture of hemostasis and cutting** (Table 8-14)

## Complications

- Thermoelectric burns at site of current exit may occur if the patient is not properly grounded
- Minimize distance a current travels in a patient's body by applying grounding pad to a highly vascularized surface in proximity to operative site
- Avoid positioning any implantable monitoring devices between the active and dispersive electrodes

## Fire hazards

- Bowel gas (methane) → exercise caution when using electrosurgery in perianal area



**Table 8-14.** Summary of Methods of Electrical Hemostasis

Type	Current	Voltage	Amperage	Terminal	Waveform	Tissue Destruction
Electrocautery	Direct	—	—	N/A	None	++++
Electrodesiccation	Alternating	High	Low	Monoterminal	Markedly Damped	+++
Electrofulguration	Alternating	High	Low	Monoterminal	Markedly damped	++
Electrocoagulation	Alternating	Low	High	Biterminal	Moderately damped	++++
Electrosection	Alternating	Low	High	Biterminal	Undamped	Minimal

- Aluminum chloride is flammable → must wash off
- Oxygen should be temporarily disabled if operative site is in close proximity to the oxygen source
- Avoid alcohol preps; use chlorhexadine or povidone-iodine instead

### Implantable electronic devices

- **Pacemakers and ICDs**
  - Most modern (1980s and on) implantable devices are resistant to external electromagnetic signals; however, there remains a theoretical risk of disturbance
  - ICDs are more sensitive than pacemakers to electromagnetic interference (because of the presence of sensing circuits)
  - Electrocautery can be used to eliminate 100% of the risk of interference
  - Electrosurgery using **biterminal** (often erroneously referred to as “bipolar”) forceps (most common way to address this issue) is also less likely to cause electromagnetic interference
  - Magnet devices are often used during electrosurgery → pacer stops paying attention to all electrical signals → paces at a preset rate
  - In cases in which biterminal forceps cannot be used or are unavailable, caution should be taken:
    - Direct the path of current away from implantable devices
    - Do not position implantable devices between the active and dispersive electrodes
    - Use short bursts of energy (<5 seconds and spaced >5 seconds apart)
    - Use lowest effective power settings
    - Avoid electrosection (highest risk!)
    - Do not use within 5 cm of implantable device
    - Have a crash cart and ACLS-trained staff ready
  - In cases of uncertainty → cardiology consultation
- **Noncardiac implanted electronic devices**
  - Examples: deep brain stimulators, spinal cord stimulators, vagal and phrenic nerve stimulators, gastric stimulators, and cochlear implants
  - In contrast to ICDs, patients are usually equipped with an external remote control to power these devices off

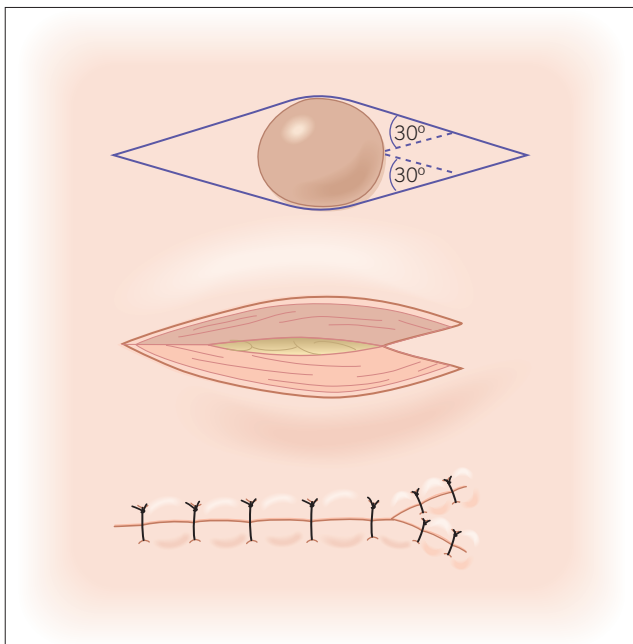
## 8.8 CRYOSURGERY

- Application of low temperature substances → cellular injury, sloughing of damaged tissue, and subsequent healing
- Mechanism of action:
  - Extracellular dehydration: results from formation of **ice crystals** first in the extracellular space causing an extracellular hyperosmotic gradient that **dehydrates** the adjacent cells
  - Membrane rupture: occurs from continued freezing, which causes **intracellular ice crystal** formation and eventual membrane rupture
  - Vasoconstriction: results from initial freezing → causes further damage through anoxia
  - Vasodilation: after thawing, compensatory vasodilation releases harmful free radicals into affected tissue → further tissue damage
- Specific cryogens:
  - **Liquid nitrogen (boiling point: –196°C)**: most common
  - Solid carbon dioxide (boiling point: –79°C): occasionally used for chemical peels
- Temperature required for cell death (boards favorite!):
  - By cell type:
    - Melanocytes (most sensitive): –5°C
    - Keratinocytes: –20°C to –30°C
    - Fibroblasts (least sensitive): –35°C to –40°C
  - Benign vs malignant
    - Benign: –25°C
    - Malignant: –50°C
- Optimal freezing technique = **rapid freezing** + **slow thawing** (favors **intracellular** ice formation)
- Delivery techniques
  - Open technique: most commonly performed; liquid nitrogen is released through tips, needles, cannulas, or cones
  - Chamber technique: modification of “open technique”; typically used only for malignancies; cryogen is released into a chamber → turbulence within the chamber → **lower temperatures achieved, and in shorter amount of time** than w/ open technique
  - Closed technique: uses a probe to deliver the thermal insult; attached directly to the cryogen line and is a closed system (thus its name)

- Intralesional technique: cryogen is injected directly into tissue via either a cannula or needle

## 8.9 EXCISIONS

- Indications: biopsy, removal of benign and malignant lesions, and scar revision
- Design: closure of a circle results in large standing cones on each side of the closed wound → therefore, most excisions are executed in a fusiform fashion
  - Apical angles: angles at either end of the excision; **ideally  $\leq 30^\circ$**  in order to avoid formation of standing cones
  - **Length:width ratio** should be  $\geq 3:1$
  - Generally, place excisions **parallel to relaxed skin tension lines**
- Variations:
  - Crescent excision: when one side of excision is designed longer than the other, a curved/crescent shape will result; common uses: sites where relaxed skin tension lines are curvilinear (**cheek and chin**)
  - M-plasty (Fig. 8-14): used to **shorten length** of excision such that the incision does not extend into an undesired location; common uses: **near free margins** (perioral and periocular regions)
  - S-plasty ("lazy S"): ↑**total length of scar**, but the linear distance between two apices remains same as linear closure; **redistributes tension** along different vectors → ↓tension in central portion of scar → ↓risk of centrally depressed scar, ↓dehiscence, and



**Figure 8-14.** M-plasty. Instead of completing the ellipse, the dashed lines are incised as shown, reducing the length of the scar. (From Rohrer TE, Cook JL, Nguyen TH. Flaps and Grafts in Dermatologic Surgery. Elsevier. 2007)

↓**contraction of scar**; common uses: **convex surfaces** (forearm and shin) and excisions that cross over a joint (elbow and knee)

- Lip wedge excision: full-thickness excision of the lip with layered repair; may be used to repair defects up to **1/3 of the length of lower lip**; must **mark vermillion border before closure** → ensures precise realignment; close lip in layered fashion in the following **order (high yield!)**:
  - Submucosal layer: use silk or polyglactin 910, bury knots away from oral cavity
  - Orbicularis oris muscle: use polyglactin 910; critical step → maintains competence of oral sphincter
  - Dermis and subcutaneous tissue: use polyglactin 910; start by reapproximating vermillion-cutaneous border
  - Epidermis: use nylon w/ hyper-eversion to prevent depressed scar
- Standing cones ("dog ears"):
  - Causes: apical angles that are too wide ( $>30^\circ$ ), length:width ratio  $<3:1$ , unequal lengths on each side of wound, convex surfaces, and insufficient undermining at wound apices
  - Repair options ("dog ear repairs"):
    - Extending incision: ↑excision length allows for redistribution of excess skin
    - M-plasty: removes standing cones
    - Rule of halves: standing cone is redistributed along entire excision length by "halving" it throughout
    - Excision of a Burow's triangle: a triangle of tissue removed from the side of the wound with the standing cone
- Closure types:
  - Simple closure: one layer of sutures (epidermal closure only)
  - Layered closure: two or more layers (epidermal + dermal, SQ or fascia) of sutures → ↓tension on wound edges, ↓dead space (results in ↓hematomas and ↓seromas), and improved cosmetic outcomes
- **Undermining planes (Boards Favorite!)**:
  - Trunk/extremities: mid-deep fat (for small or superficial defects), or just above deep fascia (larger excisions and invasive melanomas)
  - Face: undermining in superficial subcutaneous plane (**superficial to SMAS**); **preserves motor nerves**, which are all deep to SMAS
    - However, optimal undermining planes vary by facial subunit
  - Optimal undermining planes by facial subunit:
    - Cheek: mid subcutaneous plane → avoids transecting parotid duct, buccal and zygomatic branches of CN7, and vascular structures
    - Ear: given the near lack of adipose tissue, dissection is always just above **perichondrium**
    - Eyebrow: subcutis, **deep to hair bulbs** → minimizes eyebrow hair loss
    - Eyelid: immediately above orbicularis oculi muscle (because there is minimal subcutaneous tissue)

- Forehead: deep subcutaneous plane, **just above frontalis** (small, superficial wounds); occasionally undermine in subgaleal plane (large or deep wounds) → superficial SQ undermining preserves sensory nerves; subgaleal plane is avascular
- Lateral neck: superficial subcutaneous plane, above spinal accessory nerve → avoids Erb's point
- Lip: Immediately above orbicularis oris muscle → avoids cutting into vascular orbicularis muscle and branches of labial artery
- Mandible: superficial subcutaneous plane, above marginal mandibular nerve
- Nose: submuscular fascia/**periosteum/perichondrium** (deep to SMAS/nasalis muscle) → relatively avascular plane
- Scalp: **subgaleal** → avascular plane
- Temple: **superficial subcutaneous plane** → avoids transection of temporal branch of facial nerve and temporal artery
- Wound healing (see [Basic Science](#) chapter)
- **Wound strength following surgery never returns to 100%**; dehiscence risk is highest at time of suture removal (1 to 2 weeks)
  - 1 week = 5%
  - 2 weeks = <10%
  - 1 month = 40%
  - 1 year and beyond = **80% (maximum strength)**
- Surgical margins:
  - Melanoma:
    - Melanoma in situ → **0.5 cm–1 cm**
    - Breslow depth <1 mm → **1 cm** WLE to deep fat or fascia (variable)
    - Breslow depth 1–2 mm → **1–2 cm** WLE to fascia
    - Breslow depth <2 mm → **2 cm** WLE to fascia
  - BCC: **4 mm** margins for most tumors; **0.6–1 cm** margins or Mohs for high-risk BCC
    - High-risk BCC (any one feature): >2 cm diameter on any site, >1 cm diameter on face/neck/scalp, >0.6 cm diameter on high-risk area ("**H-zone** of face"), poorly defined and aggressive histology (**infiltrative, morpheiform, micronodular, and basosquamous**), recurrent, at site of prior radiation/scar, perineural/perivascular invasion, and immunosuppressed status (CLL, HIV, or hematologic malignancy)
  - SCC: **4 mm** margins adequate for most low-risk SCC; high-risk SCC is best managed with 0.6 cm margins or Mohs
  - DFSP: **2–3 cm** margins extending at least to fascia is recommended, but is a/w ↑recurrence rate relative to Mohs

## 8.10 MOHS SURGERY

- Mohs micrographic surgery (MMS): specialized method of skin cancer removal that provides complete 360° (circumferential) microscopic margin control; by definition, both the surgery and microscopic evaluation must be performed by same provider
- Advantages:
  - Allows for microscopic evaluation of 100% of the excision margins (vs <1% w/ "breadloafing" technique used for standard elliptical excisions) → **↑cure rates** because of ↓false negative margins
  - **Tissue sparing** (smaller margins can be taken w/ confidence that the tumor is clear)
  - Compares favorably in terms of **cost effectiveness** relative to other treatments
- MMS offers superior cure rates for most skin cancers, including rare forms:
  - BCC/SCC: 97%–99% for primary lesions (vs 93% for conventional excision) and 90%–95% cure rate for recurrent lesions (vs 80% for conventional excision)
  - DFSP (**treatment of choice**): 98%–100%
  - MMIS, including lentigo maligna: >98% cure rate
  - AFX: 95%–100%
  - Microcystic adnexal carcinoma: 90%–95%
  - EMPD: 85%
  - Leiomyosarcoma (superficial): >90%
  - Sebaceous carcinoma: >90%
  - Erythroplasia of Queyrat: >90%
  - Others: bowenoid papulosis, basosquamous carcinoma, verrucous carcinoma, various adnexal carcinomas, Merkel cell carcinoma (not generally recommended), and angiosarcoma (not generally recommended)
- Tumor must have a contiguous growth pattern to be amenable to Mohs
- Essentials steps of Mohs technique:
  - Clinically apparent residual tumor/biopsy site is debulked with curette or scalpel
  - **Beveled excision (scalpel held at 45° angle)** of tumor plus a small (1–2 mm) margin of normal-appearing skin
  - Hash marks ("notches") are placed on excision specimen and surrounding nonexcised skin to assist w/ orientation
  - Excised specimen may be divided into two or more pieces (optional)
  - Excised specimen is inked with two or more colors
  - Histotechnician flattens tissue to ensure that the **epidermis lies in the same plane as the deep tissue** → allows for horizontal processing of slides (stain = **H&E or Toluidine blue**) → enables simultaneous microscopic evaluation of superficial and deep margins
  - Surgeon evaluates slides for residual tumor
  - If tumor is present, the site is marked on the Mohs map, and steps two to seven are repeated until tumor has been eradicated
  - Once tumor is cleared, surgeon discusses reconstructive options w/ patient
- Indications ([Table 8-15](#))

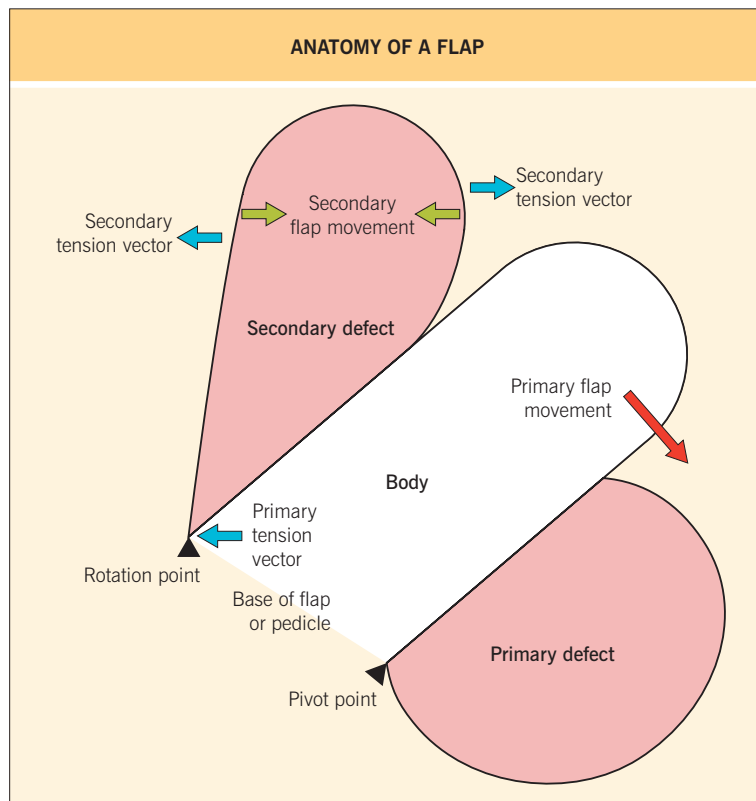
**Table 8-15.** Indications for Mohs Surgery for Nonmelanoma Skin Cancer

<b>Tumor characteristics</b>
Recurrent
High-risk* anatomic location (periorbital, perinasal, periauricular, perioral, and hair-bearing scalp)
Other anatomic sites where tissue preservation is imperative (digits and genitals)
Aggressive histologic subtypes:
Morpheaform (sclerosing), micronodular, or infiltrating BCC
High-grade, poorly differentiated and/or deeply penetrating SCC
Infiltrating, spindle cell SCC
Perineural invasion
Large size (>2 cm diameter)
Poorly defined clinical borders (lateral and/or deep)
Rapid growth
<b>Characteristics of background skin</b>
Prior exposure to ionizing radiation
Chronic scar (Marjolin's ulcer)
Site of positive margins on prior excision
<b>Patient characteristics</b>
Immunocompromised
Underlying genetic syndrome, e.g., xeroderma pigmentosum, nevoid BCC (Gorlin) syndrome, or Bazex-Dupré-Christol syndrome
BCC, basal cell carcinoma; SCC, squamous cell carcinoma
*High risk for recurrence.
(From Bologna JL, Jorizzo JL, Rapini RP. <i>Dermatology</i> , 3rd Ed. Elsevier. 2012)

## 8.11 FLAPS

- **Indications:**
  - Defects that will heal poorly by secondary intention
  - When linear repair would compromise function, result in excessive tension, or distort a free margin
  - To maintain three-dimensional contour when there is significant tissue loss
- **Advantages:**
  - Excellent color, texture, and thickness match, as the skin is recruited from adjacent tissue reservoirs
  - Ability to redirect tension vectors
  - Can be used to cover cartilage/bone because of reliable blood supply
  - Rapid healing
  - Replaces volume when there is significant tissue loss
- **Disadvantages:**
  - Poor design/surgical technique can lead to functional compromise, free margin distortion, poor esthetic outcome, and postoperative complications
  - Geometric scar lines may be readily apparent if not concealed within relaxed skin tension lines
- **Definitions (Fig. 8-15):**
  - Primary defect: operative wound that requires repair, usually following tumor removal at this site
  - Secondary defect: operative wound created by flap elevation and closure of primary defect
  - Primary lobe: portion of flap intended to cover primary defect
  - Secondary lobe: portion of flap intended to cover secondary defect
  - Primary movement: motion of flap movement required to close primary defect
  - Secondary movement: motion of flap movement required to close secondary defect
  - Primary tension vector: direction of force resisting the movement of the flap body
  - Secondary tension vector: direction of force created by closure of donor site defect
  - Pedicle (flap base): vascular base of flap → provides blood flow to flap
  - Body: tissue that is being “flapped” onto the primary defect
  - Flap tip: portion of flap furthest away from the blood supply/pedicle → area at **highest risk for necrosis**
  - Pivot point: point on the base of the flap around which the flap transposes/rotates → critical to **undermine this area to obtain optimal flap movement**
  - Flap size (used for billing purposes): entire surface area of flap elevation + surface area of primary defect
  - **Key stitch:** critical **initial stitch** required to move the flap onto the primary defect
  - **Axial pattern flap:** flaps based on a named vessel → most reliable; includes **paramedian forehead flap** (supratrochlear artery), **dorsal nasal rotation “Rieger” flap** (angular artery), and **Abbe cross-lip flap** (labial artery)
  - **Random pattern flap:** flaps with unnamed musculocutaneous arteries within pedicle; elevated portion of flap is perfused by **anastomotic subdermal and dermal vascular plexuses**; includes all flaps not listed above
- There are many ways to classify flaps (primary motion, blood supply, shape, and eponymous name), however, they are **best classified according to primary motion**:
  - **Sliding:** flap slides into place with linear or curvilinear motion; redundant tissue can be excised anywhere along length of flap; **main tension vector = opposite direction of flap movement**; key stitch closes **primary** defect (approximates flap edge to opposite edge of primary defect)
    - Advancement flap (Table 8-16):
      - ◆ Mechanics: **does not redirect** primary tension vector
      - ◆ Goal: **redistribute Burow’s triangle away from free margins** (eyelid, ear, lip, and alar rim) → move to a more functionally/cosmetically desirable location
      - ◆ Disadvantages: **limited by degree of elasticity of surrounding tissue** → suboptimal for large defects that lack abundant adjacent tissue reservoir/laxity
    - Rotation flap (Table 8-17):
      - ◆ Mechanics: **redirects primary tension vector** along an arc adjacent to primary surgical defect while simultaneously creating a secondary defect along the flap arc
      - ◆ Goal: take advantage of tissue reservoir/laxity at a distance from primary defect
      - ◆ Disadvantages: there is a **functional loss of flap length and height** when flap is rotated onto





**Figure 8-15.** Anatomy of a flap. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

defect → length of flap arc must be much longer than width of primary defect and height of flap must be taller than height of primary defect; is a heavy flap and prone to causing unwanted secondary tension vectors → may result in distortion of free margins (ectropion) if not carefully executed → may require tacking sutures to periosteum to minimize risk

- ◆ Main uses: large defects on medial cheek; large defects on inelastic skin (scalp); areas w/ curved RSTLs (chin and along mental crease); redistribute tension away from free margins (lower eyelid, nasal tip, and upper lip)

- **Lifting:** flap is lifted and transposed ("leapfrogged") over normal intervening skin; has both **pivotal** and **rotational** movements; **redirects primary tension vector** to donor site; goal is to use nearby, but "nonadjacent," tissue reservoir ("nonadjacent": intervening normal skin is present between flap donor site and primary defect) in order to close primary defects at sites that have minimal inherent laxity (nose, medial canthus, and ear); key stitch varies depending on specific flap

○ Transposition (single stage) (Table 8-18)

- ◆ Mechanics: **redirects primary tension vector** onto donor site → results in loose flap of skin that can be "plopped onto" primary defect → primary defect closed under minimal to no tension
- ◆ Goal: utilize nearby tissue reservoirs in order to close defects at sites that have minimal inherent laxity

- ◆ Disadvantages: prone to **pincushioning**/"trapdooring" (→ must widely undermine to prevent); technically challenging

○ "Interpolation" (two stage transposition) flaps (Table 8-19)

- ◆ Mechanics: same as single-stage transposition flaps, but retains thick vascular pedicle (either **random pattern** or **axial**) to ↑ blood flow → allows for ↑↑↑ **flap length:width ratio** (>4:1 **maximum ratio** seen with most other flaps), and coverage of very large defects; **pedicle typically divided and inset at 3 weeks**

- ◆ Goal: utilize nearby tissue reservoirs in order to close defects at sites that have minimal inherent laxity

- ◆ Main uses: large defects on nose, large helical rim defects, and large lip defects

• Sliding flaps (noteworthy **key stitches** marked with star)

- Unilateral advancement flap ("O to U" or "U-plasty") (Fig. 8-16)
- Bilateral advancement flap ("H-plasty") (Fig. 8-17)
- Bilateral advancement flap ("A-to-T") (Fig. 8-18)
- Burow's advancement flap, crescentic advancement flap (Fig. 8-19)
- V-to-Y advancement flap (formerly, "island pedicle flap"): vascular supply derived from nonundermined subcutaneous pedicle (Fig. 8-20)
- Rotation flap (Mustarde type) (Fig. 8-21)

• Lifting flaps

- Rhombic flap (and variants) (Fig. 8-22)
- Bilobed transposition flap (Fig. 8-23)

*Text continued on p. 442*

Table 8-16. Advancement Flaps

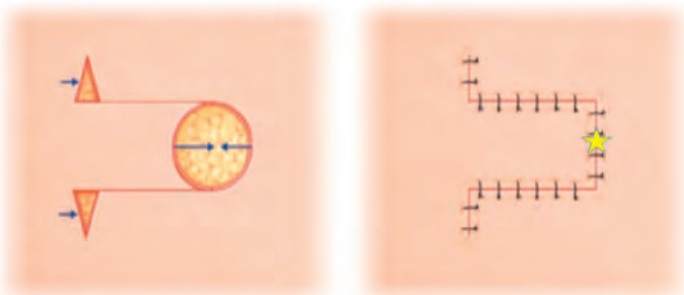
Flap Category (Variants/Other Names)	Design	Common Uses	Comments
Unilateral Burow's advancement (A → L, O → L)	Displaces one of the Burow's triangles to a more cosmetically desired location, away from free margins or junction of two cosmetic subunits	Suprabrow (displaces Burow's lateral to eyebrow) Off-center nasal dorsum/tip (maintains nasal symmetry) Lateral upper cutaneous lip (displaces Burow's into NLF)	Does not provide much added laxity relative to linear closure
Unilateral crescentic advancement (cheek to nose crescentic)	Variant of A → L where a crescentic standing cone is removed within flap body → eliminates need to remove one of the two Burow's triangles	Suprabrow (hides incision above eyebrow hairline) <b>Cheek to nose advancement:</b> medium-large defects of nasofacial sulcus, nasal sidewall, and lateral supraalar region (hides incision in NLF and/or alar crease)	Area under surrounding crescent must be widely undermined to enable flap movement
Unilateral O → U advancement (helical rim advancement)	Incisions and Burow's triangles oriented in same direction away from defect → a square-shaped flap is advanced onto defect	Suprabrow (hides one incision line above browline and other in a horizontal forehead crease) Helical rim advancement (used for deeper rim defects not amenable to grafting or second intention)	Smaller pedicle → more prone to ischemia <b>Hyper-evert</b> helical rim flaps → prevents notching
Bilateral A → T advancement (O → T)	Divides one of the two standing cones into two smaller Burow's triangles; two opposing flaps are bilaterally advanced onto defect	Similar to A → L, but can cover larger defects Chin (hides flap incisions in mental crease)	—
Bilateral O → H advancement	Essentially a double O → U flap, w/ mirror-image flaps on either end of primary defect	Eyebrow, forehead	Disadvantages: multiple incision lines, <b>forehead numbness</b> (as a result of long horizontal incision)
Island pedicle/"kite" flap (renamed V → Y advancement)	Unlike other advancement flaps, <b>area under flap body is not undermined</b> (serves as random-pattern pedicle); periphery is undermined widely, then V-shaped island w/ pedicle is advanced onto defect; ideal <b>length:width ratio ≤4:1</b> ; <b>key stitch:</b> connects midpoint of leading edge of flap to midpoint of defect's wound edge	Small defects on nasal tip Small, deep alar defects (shark IPF) Small defects on medial upper cutaneous lip Medium to large defects on lateral upper cutaneous lip Large defects on medial cheek or nasofacial sulcus Lower eyelid defects Repair of ectropion	In reality, a portion of pedicle must be undermined to allow for movement, but <b>must ensure that ≥40% of pedicle remains intact</b> Disadvantages: triangular-shaped scar (often prominent); <b>trapdoor effect</b>
Mucosal advancement	Essentially a linear flap of lip mucosa; <b>undermine deep to minor salivary glands, but superficial to orbicularis muscle</b> ; undermine to gingival sulcus; flap is advanced onto vermillion defect	Vermillion lip	<b>Lip numbness</b> develops in most, but improves over time

Table 8-17. Rotation Flaps

Flap Category (Variants/Other Names)	Design	Common Uses	Comments
Unilateral rotation	Curvilinear incision w/ arc length > defect width, and arc height > defect height to compensate for loss of length as flap rotates; <b>area of pivotal restraint must be undermined</b> extensively to allow movement; <b>back-cuts</b> ↑mobility, but ↓blood flow	Upper cutaneous lip (hides incision in melolabial fold) Nose (tension vectors redirected away from alar rim)	On face, flap pedicle should be inferior-lateral to ↑lymphatic drainage → ↓flap lymphedema
Unilateral rotation, Rieger variant (dorsal nasal rotation, Hatchet flap, and glabellar turn-down)	<b>Axial flap (angular artery)</b> w/ <b>back-cut in glabella</b> ; undermine just above perichondrium; maximal points of <b>pivotal restraint = medial canthal tendon, nasofacial sulcus</b>	Medium to large (up to 2.5 cm) midline defects on lower 2/3 of nose (tip/supratip)	Disadvantages: <b>transposition of thick glabellar skin onto medial canthus (number one concern)</b> , long incision lines, potential <b>"pig-nose" deformity</b> (as a result of inadequate undermining)
Unilateral rotation, Mustarde/Tenzel variant	Laterally based rotation flap of cheek/temple; Mustarde flaps utilize entire cheek/temple reservoir; Tenzel flaps are smaller (partial-cheek)	Mustarde: larger lower lid defects (≥50%) Tenzel: smaller, partial thickness defects of mid to lateral lower lid (<50% of lid)	<b>Tacking sutures to lateral orbital rim periosteum</b> → ↓ectropion risk
Bilateral rotation (O → Z)	Double rotation flap with yin-yang shape	Large defects involving inelastic skin (mainly used for <b>scalp</b> )	Disadvantage = long, prominent incision lines (minimize w/ good galeal suturing, eversion)

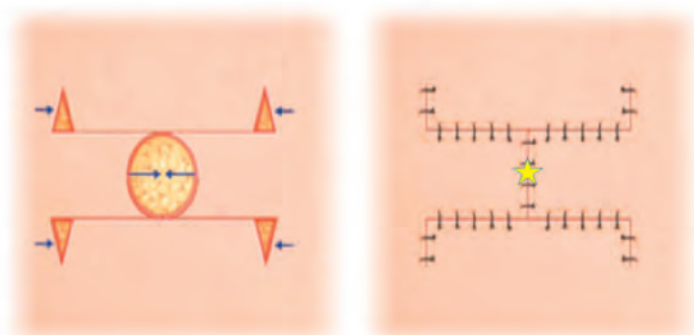
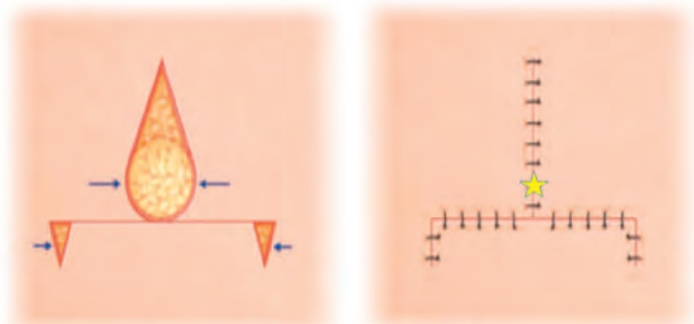
**Table 8-18.** Transposition Flaps (Single Stage)

Flap Category (Variants/Other Names)	Design	Common Uses	Comments
Rhombic	Classic design (Limberg flap: <b>parallelogram-shaped flap</b> w/ two 60° angles and two 120° angles; flap takes off from defect at 90° angle; Burow's triangle removed as a pivot point; <b>secondary defect is closed first (key stitch)</b> )	Medial and lateral canthi Cheek Upper lateral 1/3 of nose Perioral	Final suture line looks like a <b>question mark</b> <b>Eight rhombic flaps possible</b> for any rhombic-shaped defect <b>DuFourmental and Webster modifications:</b> ↓angle of flap tip → <b>shorter arc of rotation</b> → easier to close secondary defect, ↑ <b>tension sharing</b> between 1° and 2° defect, ↓reorientation of tension vectors, and ↑risk of ischemia (as a result of a narrower pedicle)
Bilobed transposition flaps (Zitelli modification)	Multilobed transposition flap that <b>redistributes tension to areas of greater tissue laxity</b> (e.g., nasal dorsum); tension is shared between all lobes; <b>1° lobe diameter = primary defect diameter; 2° lobe diameter = 1° lobe diameter</b> (or slightly smaller); flap takeoff point = midpoint of defect at a 45° angle; angle between 1° and 2° lobe also = 45° → flap has <b>overall angle of 90°</b> ; remove standing cone at pivot point; <b>undermine flap in submuscular plane to nasofacial sulcus</b> to achieve adequate movement; <b>order of closure = tertiary defect</b> (2° lobe donor site; <b>key stitch</b> ) → secondary defect (1° lobe donor site) → primary defect closed last	Distal 1/3 of nose	May use as many lobes as necessary (trilobe, tetralobe) to reach a tissue reservoir where tension will not cause distortion Risk of <b>pincushioning (trapdoor)</b> → may be because of an oversized flap, insufficient undermining, ↑bulkiness on underside of flap, flap lymphedema (self-resolves), peripheral contraction (↑risk w/ rounded flaps), or insufficient tacking of flap to wound base Original bilobed flap design was inferior to Zitelli's: used 180° overall angle (vs 90°) and did not remove standing cone at pivot point → ↑pincushioning of 1° lobe, ↑standing cone at pivot point
Banner transposition flap	Long, narrow transposition flaps w/ <b>high length:width ratio</b> (3:1–5:1); flap is raised along RSTLs and transposed 90° (or more) onto primary defect	Upper helical rim Medial canthus and nasal bridge (glabellar banner) Lateral lower lid (upper lid skin is transposed) Medial lower lid (banner flap from nasofacial sulcus)	As a result of a narrow pedicle, must ensure flap has reliable/robust blood supply to prevent necrosis Prone to <b>pincushioning (trapdoor) effect</b> → must undermine recipient site widely, undersize flap or deepen recipient bed, and use tacking sutures to ↓dead space between flap and recipient site
Nasolabial/ melolabial transposition flap	Variant of banner flap w/ 60° angle of transposition; tack pivot point to <b>piriform aperture</b> (near junction of lateral ala/isthmus of upper lip); must thin distal portion of flap extensively	Medium-sized, deep defects of nasal ala	Disadvantages: <b>blunting of alar crease (almost all cases), pincushioning</b> → minimized w/ tacking sutures, flap thinning, and wide undermining of recipient site Many cases require revision <b>Spear flap (variant):</b> used for full-thickness alar defects; same general design, but flap is folded on itself to provide internal nasal lining + external coverage
Z-plasty	Transposition flap primarily used for lengthening a contracted scar and redirecting tension; may use various angles: ↑ <b>angle size</b> → ↑ <b>length gain</b> , and ↑ <b>reorientation</b> of tension		30° angle → 25% ↑length and 40° tension reorientation 45° angle → 50% ↑length and 65° tension reorientation 60° angle → 75% ↑length and 90° tension reorientation

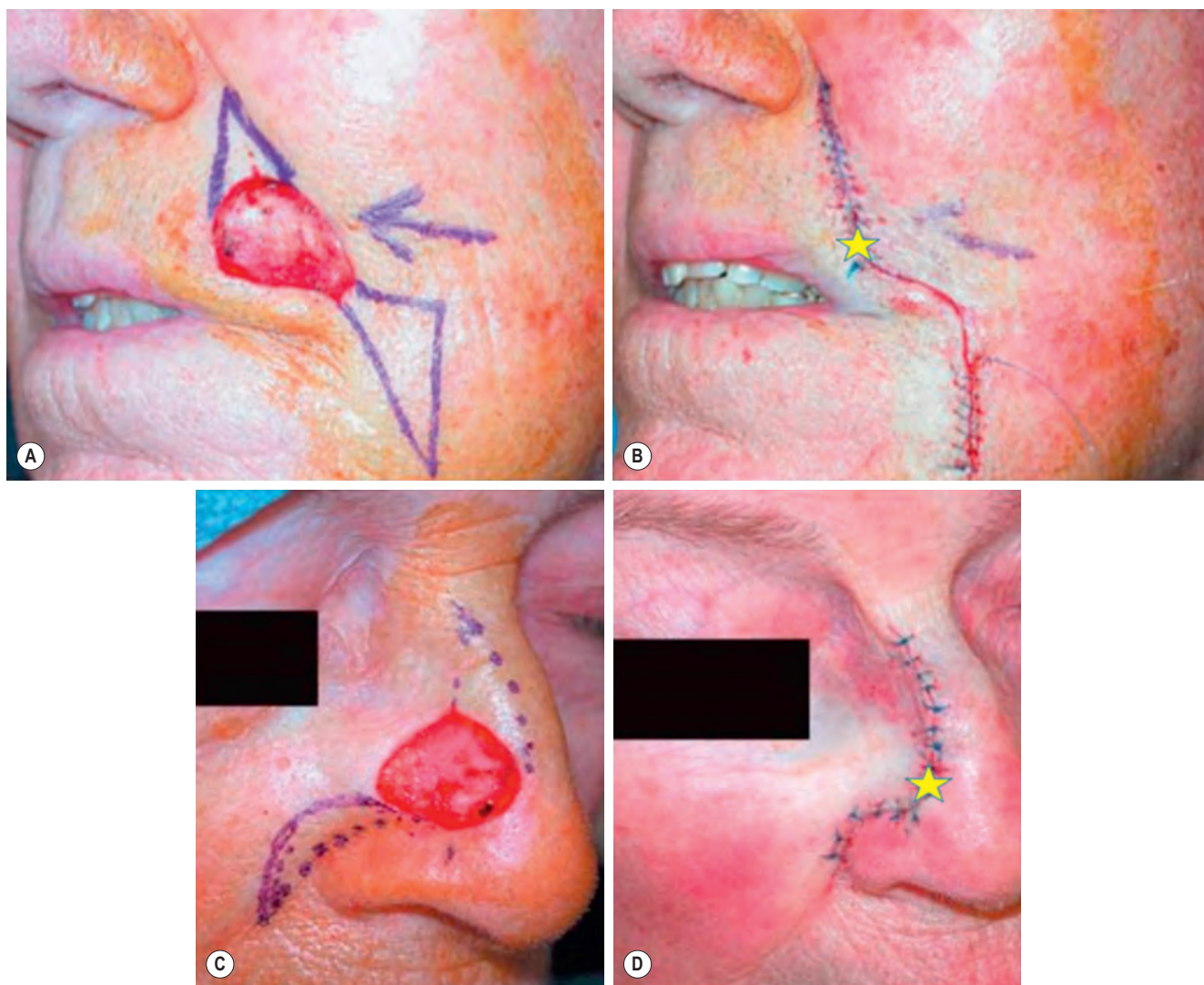
**Unilateral advancement flap****Figure 8-16.** Unilateral advancement flaps are most suitable for repair of defects within the eyebrow where scars can readily be hidden. Elsewhere it produces a complex scar and other repairs are generally favored. (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)

**Table 8-19.** Interpolation" (Two-Stage Transposition) Flaps

Flap Category (Variants/ Other Names)	Design	Common Uses	Comments
Paramedian forehead flap	<b>Axial flap</b> based on supratrochlear artery; <b>maximum length of flap = distance between orbital rim to frontal hairline</b> (if longer, will transplant hair onto nose); <b>pedicle positioned on opposite side</b> as main portion of nasal defect; pedicle oriented in vertical fashion, arising at medial eyebrow; ideal <b>pedicle width = 1.0 – 1.5 cm</b> ; flap body elevated from cephalad to caudad in a plane just above periosteum; flap tip must be extensively thinned before suturing to nasal tip; <b>pedicle is divided and inset at 3 weeks</b>	Large nasal defects	Pedicle too narrow → fails to incorporate artery → ischemia Pedicle too wide → kinking of artery → ischemia and ↓rotational ability
Abbe' lip switch	<b>Axial flap</b> based on labial artery; transfers both mucosa and orbicularis oris muscle to recipient site; <b>pedicle divided and inset at 3 weeks</b>	Large (>1/3 of lip), full-thickness defects of upper or lower lip	Most commonly used for upper lip defects, because defects involving <b>up to 1/3</b> of lower lip can be repaired via <b>lip wedge</b> Risk of microstomia and oral incompetence
Nasolabial/ melolabial interpolation flap	<b>Random pattern flap</b> perfused by small perforators of angular artery; similar in design to single-stage nasolabial transposition flap, but retains a thick vascular pedicle; extensively debulk flap tip before suturing onto primary defect; <b>pedicle divided and inset at 3 weeks</b>	Nasal ala (number one use) Large defects of upper cutaneous lip	<b>Does not blunt alar crease</b> = main advantage over single-stage transposition
Retroauricular ("book") flap	<b>Random pattern flap</b> ; a rectangular-shaped flap is raised in subcutaneous plane from retroauricular sulcus to the hairline; flap tip is thinned and sutured onto helix; <b>pedicle divided at 3 weeks</b>	Large defects of helical rim +/- loss of cartilage	Donor site may be left to heal by second intention

**Bilateral advancement flap****Figure 8-17.** Bilateral advancement flap. (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)**Classic A-T bilateral advancement flap****Figure 8-18.** Bilateral advancement flap ("A-to-T"). (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)

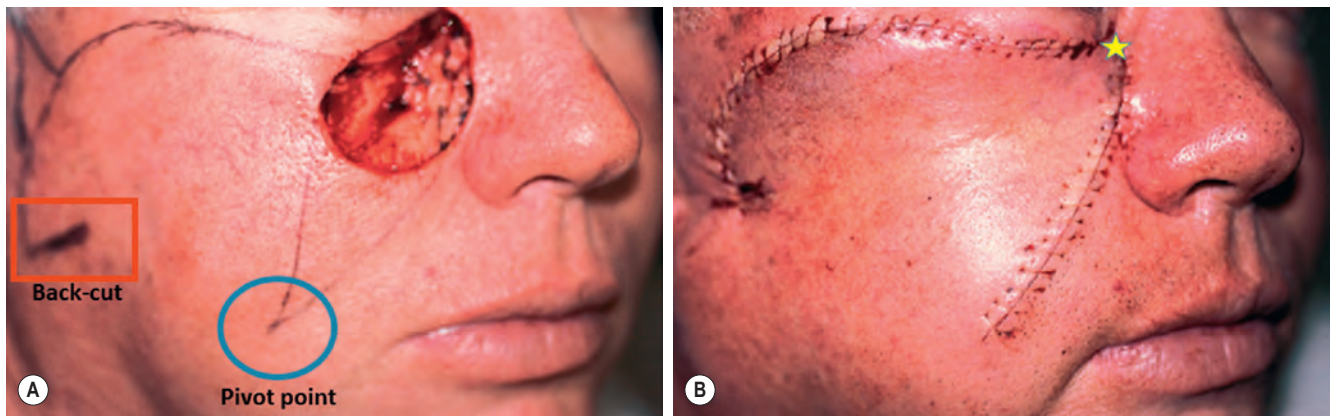




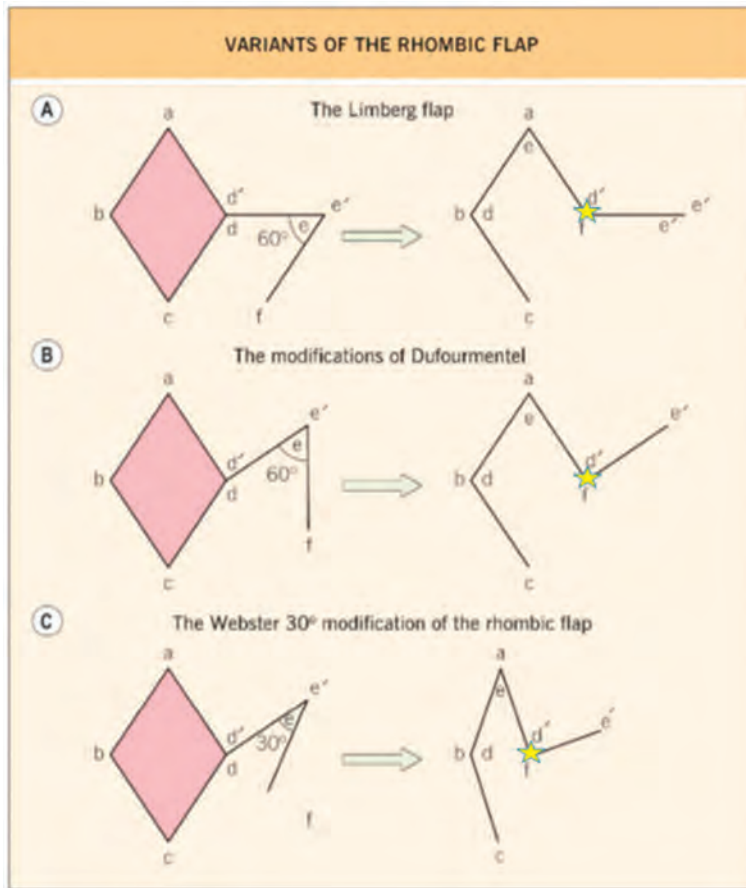
**Figure 8-19.** Burow's advancement flap (A and B); crescentic advancement flap (C and D). (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)



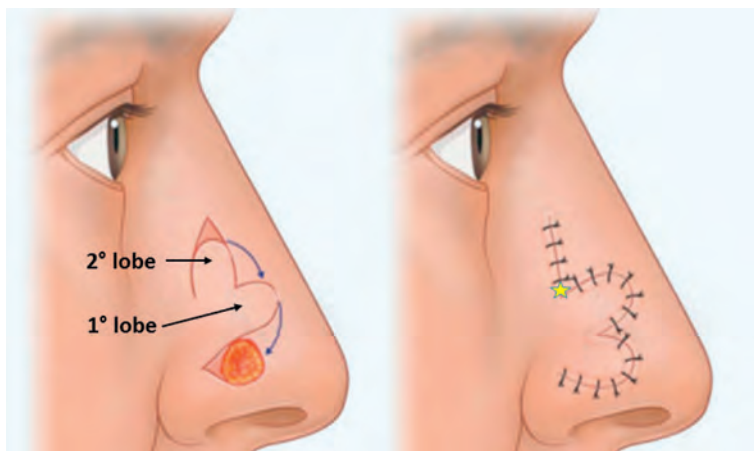
**Figure 8-20.** V-to-Y advancement flap (formerly, "island pedicle flap"): vascular supply derived from nonundermined subcutaneous pedicle. (Modified from Cook J. *Flaps and Grafts in Dermatologic Surgery*. 1st ed. Saunders; 2007 Jan:69–77)



**Figure 8-21.** Mustarde type rotation flap.



**Figure 8-22.** Rhombic flap (and variants). (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)



**Figure 8-23.** Bilobed transposition flap. (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier. 2014)



**Figure 8-24.** Single-stage nasolabial/melolabial transposition (modified banner) flap. (Modified from Robinson et al. *Surgery of the Skin*, 3rd Ed. Elsevier, 2014)

**Table 8-20.** Comparison of Graft Types Used in Soft Tissue Reconstruction

Graft Type	Tissue Match	Nutritional Requirements	Requirement for Recipient Bed Vascularity	Infection Risk	Graft Contraction Risk	Durability	Sensation	Adnexal Functions
FTSG	Good to excellent	High	High	Low	Low	Good to excellent	Good	Excellent
STSG	Poor to fair	Low	Low	Low	High	Fair to good	Fair	Poor
Composite	Good	Very high	Very high	Moderate	Low	Fair	Fair	Good
Free Cartilage	N/A	Moderate	High	Moderate	Migration or deformation possible, with subsequent resorption	Good	NA	NA

*FTSG, full-thickness skin graft; STSG, split-thickness skin graft*  
 (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier, 2012)

- Single stage-nasolabial/melolabial transposition (modified banner) flap (Fig. 8-24)

## 8.12 GRAFTS

- When a defect is not amenable to primary or flap closure → skin grafts offer a good alternative
- Four main categories of skin grafts are commonly used, each w/ their own pros and cons (Table 8-20)
- Physiology
  - Imbibition (24–48 hours):** first stage, ischemic period
    - Fibrin attaches graft to bed
    - Graft is sustained by passive diffusion of nutrients from plasma exudate of wound bed
    - Graft becomes edematous
  - Inosculation (48–72 hours, lasts 7–10 days):** second stage
    - Revascularization resulting in linkage of dermal vessels between graft and recipient wound bed
  - Neovascularization (day 7):** last stage critical to graft survival, occurs in conjunction w/ inosculation
    - Capillary and lymphatic ingrowth from recipient to graft → revascularization complete by day 7
    - Edema begins to resolve
- Reinnervation/Maturation (starting at 2 months):** slow process that is not completed for many months to years
- Types of grafts
  - Full thickness skin graft (FTSG):**
    - Comprised of epidermis and full-thickness dermis
    - Primary goal: match donor skin w/ recipient site based on skin color, texture, thickness, degree of photo damage, and presence/absence of hair (Table 8-21)
    - Advantages: better overall appearance than STSG, retains adnexal structures (and function), better contour and texture match; greater thickness → ↓wound contracture
    - Disadvantages: ↑metabolic demand → ↑rate of graft failure
    - Oversize graft by 10%–20% to account for graft shrinkage after harvesting
    - Defatting (classic teaching): leaving fat on underside of graft has long been thought to reduce survival → most books recommend complete removal of adipose tissue on graft
      - However, recent studies suggest defatting is not necessary and skin-fat composite grafts survive extremely well, especially on nose



**Table 8-21.** Summary of Possible Full-Thickness Donor Sites for Defects in Different Locations

Defect Sites	Donor Sites
Nasal dorsum, sidewalls, tip	Preauricular region, supraclavicular region, or lateral neck (if large)
Nasal tip, ala	Preauricular region, conchal bowl, nasolabial fold
Junction of nasal dorsum/tip	Burrow's graft
Ear	Postauricular sulcus, preauricular
Lower eyelid/medial canthus	Upper eyelid, postauricular sulcus
Scalp	Supraclavicular region, lateral neck, inner upper arm
Forehead	Burrow's graft, supraclavicular region, lateral neck, inner upper arm (if large)

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Bolster dressing
  - ◆ **Purpose:** graft immobilization → ↑graft adherence to wound bed
  - ◆ Technique: a thick layer of petrolatum or antibiotic ointment is applied over graft, followed by bulky material wrapped in nonadherent gauze; tie-over sutures are then used to secure bolster dressing
- Delayed grafting
  - ◆ Useful for:
    - Deep defects that cannot be adequately filled by FTSG alone
    - Defects w/ significant amount of exposed bone or cartilage (>25% of periosteum or perichondrium is lacking)
  - ◆ Wound is allowed to **granulate for 1 to 3 weeks before delayed grafting** is performed → granulation tissue provides well-vascularized bed to promote graft survival
- Burow's graft (commonly used type of FTSG)
  - ◆ FTSG derived from skin *adjacent* to the defect, (donor skin = discarded Burow's triangle skin resulting from partial primary closure of defect) → provides excellent tissue color and texture match compared with grafts harvested from distant sites
  - ◆ Most often utilized when primary repair does not fully close the defect or if complete closure would result in distortion of free anatomic margin (e.g., alar rim, perioral, and periorbital area)
  - ◆ Also useful for defects that span two cosmetic units, as it allows primary closure of one unit and graft of the second cosmetic unit
- Refinement of FTSG w/ **dermabrasion** (~4 to 6 weeks postop) may ↑cosmesis
- **Graft necrosis:** indicated by **black color** (do not confuse w/ purple congestion phase, which is normal) → do NOT remove, serves as **biologic dressing**
- **Split-thickness skin graft (STSG):**
  - Comprised of full thickness epidermis and variable amount of dermis
- Advantages: covers larger defects (>5 cm), ↑graft survival (as a result of ↓demand for nutritional support), and easier detection of tumor recurrence
- Disadvantages: ↓cosmesis, ↑contraction (→ not recommended near free margins), lacks adnexal structures, ↓anchoring to BMZ (→ bullae within graft site), requires specialized instruments, and painful donor site
- Classified by overall thickness:
  - ◆ Thin (0.005–0.012 in)
  - ◆ Medium (0.012–0.018 in) → head and neck
  - ◆ Thick (0.018–0.030 in) → trunk and extremities
- Instruments
  - ◆ Weck blade: specialized free-hand knife with accompanying templates for various graft thicknesses
  - ◆ Zimmer: electric dermatome used to harvest large STSGs of various thickness and width
  - ◆ **Mesher:** flat bed with roller that compresses STSG on plastic template with grid-like etched pattern that puts fine fenestrations into the graft
    - Meshing enlarges size of STSGs by 25%–35% and increases flexibility
    - Allows serosanguineous drainage from recipient bed, which may otherwise interfere with graft adherence and survivability
    - Disadvantage: fenestrations often permanent → ↓cosmesis
- **Composite grafts:** modified FTSG that contains more than one tissue component, most often cartilage; dependent on bridging phenomenon (rapid revascularization) for survival
- Skin + cartilage graft: cartilage is used to **restore structural integrity**, especially of the nasal ala, to prevent anatomic distortion and alar collapse during inspiration; very high metabolic demand, **very high risk of necrosis**
  - ◆ For highly sebaceous distal part of the nose, free cartilage graft harvested from ear favored +/- delayed graft/local flap for better tissue match
  - ◆ Recommend **oversizing graft by 10%–15%** to tuck the edge into subdermal space (the "pocket") of recipient site
- Skin + fat
  - ◆ More tenuous survival than FTSGs because of reduced access to vascular supply; graft size should be 1–2 cm in maximal diameter to minimize risk of necrosis; consider delayed graft to increase likelihood of survival
  - ◆ Caution in elderly patients, smokers, and those with conditions of vascular compromise (diabetes, vasoocclusive disease, and h/o ionizing radiation at graft recipient site)
- **Xenografts:**
  - temporary grafts, usually harvested as STSG from swine; function as biologic dressings and **promote granulation**; remain in place for 7–14 days; most commonly utilized in secondary intention healing or delayed repairs



- Advantages: ↓wound care demands for patient; protect/preserve bone, cartilage, tendons, and nerves; ↓postoperative pain at granulating site
- Disadvantages: must be replaced 1 to 2 weeks after application, contraindicated in patients with pork allergy, and is malodorous after 10–14 days

### 8.13 SURGICAL COMPLICATIONS AND MEASURES TO AVOID THEM

- **Infection**
  - Vast majority of wounds created during cutaneous surgery are classified as “clean” → low infection rates (1%–2%)
  - Second intention wounds paradoxically have lower risk than sutured wounds (Table 8-22)
  - Presents 4–8 days postoperatively
  - Symptoms: **rubor** (erythema, often extending asymmetrically from suture line), **dolor** (pain), **calor** (warmth), and **tumor** (swelling); may also have purulent discharge, lymphangitic streaks, fevers, and chills
  - **Staphylococcus aureus** is #1 culprit overall
    - **Pseudomonas** is common on ear
    - Always obtain wound culture
  - Treatment:
    - Abscesses: traditional dogma is to incise, drain, and pack the infected wound until it heals by second intention; recent studies suggest that wound may be sutured immediately following drainage
    - Surgical site infection without abscess: start antibiotics (first generation cephalosporin, β-lactamase-resistant penicillin, or penicillin/β-lactamase inhibitor combination); consider clindamycin, doxycycline or TMP-SMX if high index of suspicion for MRSA
  - Differential diagnosis: contact dermatitis (itchy) and inflammatory suture reaction (usually presents later)

- Prevention:
  - Surgical site infections: use sterile technique, minimize wound tension, and consider antibiotic prophylaxis if operating on inflamed skin or high-risk areas (lower legs and groin)
  - Perioperative antibiotic prophylaxis recommendations for prevention of infective endocarditis and prosthetic joint infections (Table 8-23, Fig. 8-25)

#### ● **Bleeding**

- Bleeding may lead to hematoma, ↑risk of infection, ↑wound tension, and dehiscence
- Highest risk = **first 48 hours** postoperatively (majority within first 24 hours, after epinephrine wears off)
- Patient risk factors:
  - Aspirin: affects platelets for 6–10 days; withhold for 10 days before and 5–7 days after surgery as long as it does not impose a risk for stroke or myocardial infarction
  - Thienopyridines (e.g., clopidogrel and ticlopidine): do not stop these medications if patient is taking for cardiac or neurologic indications
  - Warfarin: check INR to assure it is <3 before proceeding with surgery
  - Herbs and supplements that enhance anticoagulation effects of warfarin and/or inhibit platelet adhesion: **feverfew, fish oil, garlic, ginger, ginkgo, ginseng, bilberry, chondroitin, vitamin E, licorice, devil’s claw, danshen, dong quai, and alcohol**
- Prevention: consider minimizing undermining; consider linear closure rather than flap; drain placement; apply pressure dressing immediately after procedure and leave on for ≥24 hours

#### ● **Hematoma**

- Gelatin-like clots formed by blood collecting in “dead space” of wound; presents with **pain, swelling, and red-purple discoloration**
- Hematomas may lead to dehiscence, necrosis, and infection

**Table 8-22.** Wound Classification

Class	Attributes	Percent That Develop Infections
Clean (Class 1)	Technique immaculate Noninflammatory	1–4
Clean-contaminated (Class 2)	Small breaks in technique Gastrointestinal, respiratory or genitourinary tracts entered without gross contamination	5–15
Contaminated (Class 3)	Major breaks in technique Gross contamination from gastrointestinal, genitourinary, or respiratory tracts	6–25
Dirty and/or infected (Class 4)	Wound with acute bacterial infections ± pus	>25

*Technique in the table refers to sterile surgical technique.  
(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)*

**Table 8-23.** Antibiotics for Prevention of Surgical Site Infections

Method of Administration	Effect Based on Available Data
Topical antibiotics (postoperative)	No difference compared with white petrolatum
Topical antibiotics (preoperative nasal mupirocin for <i>Staphylococcus</i> carriers)	↓infections relative pre- and postoperative oral antibiotics
Locally injected antibiotics (mixed w/ local anesthetic)	↓infection rate
Preoperative systemic antibiotic prophylaxis (single dose)	Effective; recommended for patients at risk of infective endocarditis or prosthetic joint infection
Postoperative systemic antibiotic prophylaxis	Cohort studies suggest a minor benefit, but no large RCTs

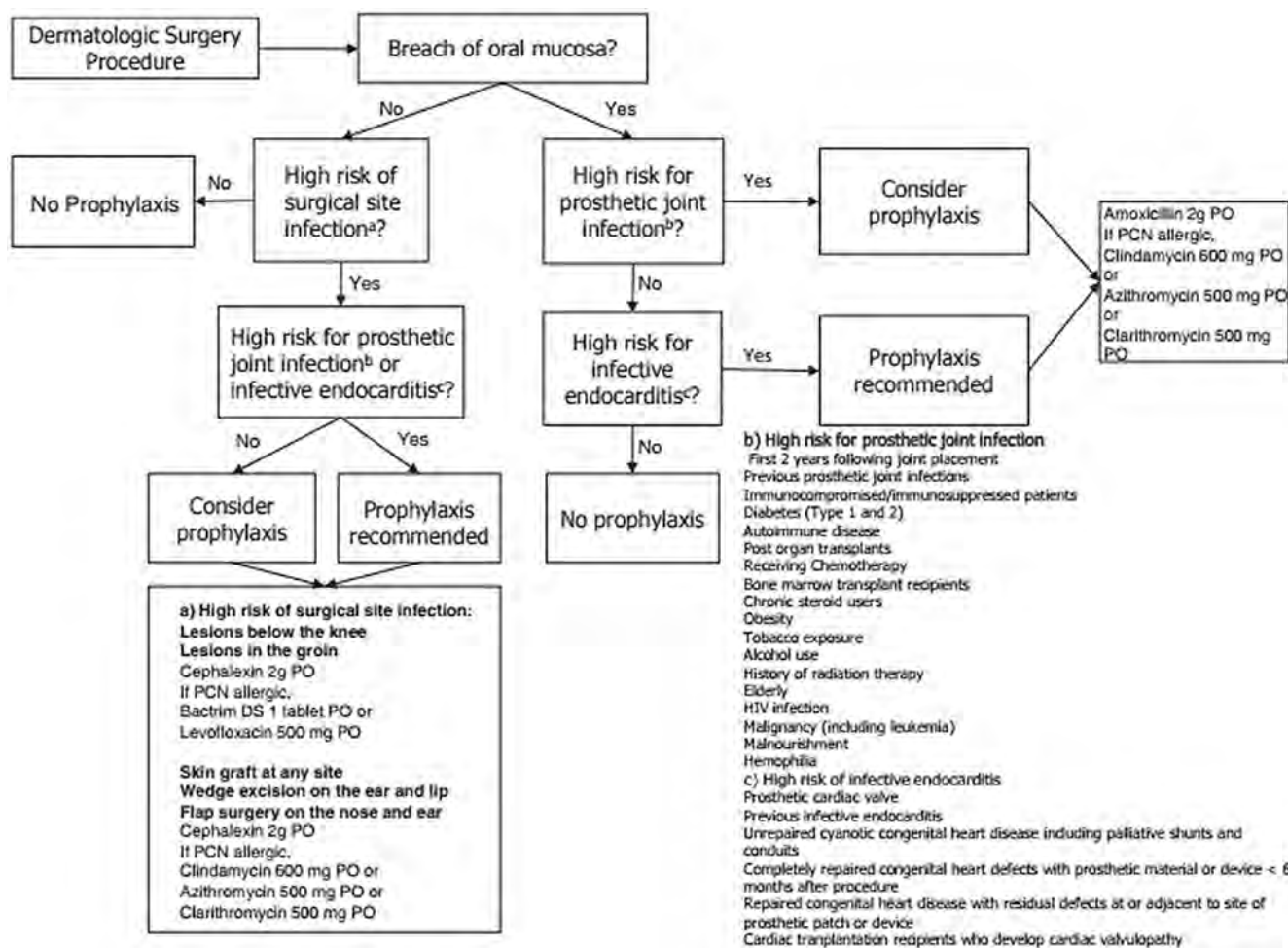


Figure 8-25. Updated prophylaxis algorithm for dermatologic surgery. (From Dermatol Surg. 2013 Nov;39(11):1592-601, Bae-Harboe YS, Liang CA)

- Small hematoma → **pressure sensation**
  - Small and stable hematomas resolve on their own; no intervention needed but may use warm compresses to hasten resolution
- Large expanding hematoma → **acute throbbing pain**
  - Requires wound exploration, irrigation, evacuation of hematoma, and/or drain placement
  - Expanding hematomas in **periorbital region** (→ blindness), and **neck** (→ airway compromise) are considered **medical emergencies**
- Early hematomas (**first 48 hours postop**) are fluctuant → easy to aspirate with a 16 or 18 gauge needle
- Organized hematomas (**≥1 week postop**) are thick, fibrous, and adherent to surrounding tissue → cannot be aspirated
  - ~**Two weeks postop**, organized hematomas undergo **liquefaction** → can be aspirated, or left alone to self-resorb (over many months)
  - Bromelain (Ananase, Delta Labs; Traumanase, Aventis): oral concentrate of proteolytic enzymes derived from the pineapple plant → expedites hematoma resolution
- Ischemia/necrosis
  - Earliest sign of ischemia is **pallor**
    - **Arterial insufficiency**: ↓skin temperature, lack of bleeding following pinprick test; flaps can remain viable for up to 12–14 hours
    - **Venous congestion**: cyanotic-purple skin color, ↑dark purple bleeding following pinprick test; flaps undergo rapid necrosis (<3–4 hours)
  - Caused by: hematoma, infection, and ↑wound tension
  - Risk factors:
    - Patient-related: **smoking**, nicotine-containing products
    - Procedure-related: extensive superficial undermining, postoperative edema, sutures tied too tightly, and insufficient or excessive electrocoagulation
  - Prevention: appropriate intraoperative hemostasis, minimize wound closure tension
  - Treatment: suture replacement (↓tension), elevation (↓edema), heat application (↑circulation), and hyperbaric oxygen (↑oxygenation)
    - **Do NOT debride necrotic tissue** (unless shows signs of infection), since it serves as a biologic dressing

- Dehiscence
  - Separation of wound edges as a result of excessive tension, infection, or necrosis
  - Highest risk = **time of suture removal**
    - Consider removing sutures in stages if prolonged support is needed
  - Treatment:
    - Classic teaching: **resuture if within 24 hours**; if  $\geq 24$  hours  $\rightarrow$  let it granulate on its own
    - Recent literature supports resuturing if no infection, hematoma, necrosis, or after underlying complication has been treated
- Abnormal healing
  - Chondritis: **painful**; may occur after any ear procedure involving cartilage; may be a/w *PSEUDOMONAS* infection; treat w/ NSAIDs + **quinolones** (if infected)
  - Contour irregularities: treated w/ **dermabrasion (6 weeks postoperatively)** ablative laser, or excision
  - Ectropion:
    - Cause: downward tension on lower lid
    - Risk factors: poor recoil on “**snap test**”
    - Prevention: **tacking sutures** to periosteum and FROST suspension sutures
  - Eyebrow elevation: avoid closures that elevate brow  $>3$  mm (unlikely to self-resolve)
  - Free margin distortion: avoided w/ proper surgical design
  - Keloids: often patient- and site-specific (anterior neck, chest, and scars crossing jawline); treat w/ intralesional corticosteroids
  - Pincushioning/trapdoor deformity:
    - Risk factors: frequently as a result of concentric contractile forces  $\rightarrow$  flaps w/ curved incision lines have highest risk (e.g., **bilobed flaps** and **nasolabial transposition flaps**)
    - Prevention: **wide undermining** appropriate sizing of flap, ensure adequate flap adherence to wound base
    - Treatment: intralesional corticosteroids (into SQ) +/- scar revision
  - Spitting sutures:  $\uparrow$  risk w/ Vicryl or **sutures placed superficially in dermis**, occurs 1–3 months postop; remove if possible
  - Suture granulomas:  $\uparrow$  risk w/ Vicryl, occurs 1–3 months postoperatively; self-resolves without sequelae, but may treat w/ intralesional steroids
  - Telangiectasias (neovascularization): treated w/ pulsed dye laser
  - Thickened scars: treated w/ massage or intralesional corticosteroids
  - “Track marks”: do not tie sutures too tightly or leave in place for too long; consider running subcuticular epidermal closure
  - Webbed or contracted scars: consider Z-plasty revision
- Motor nerve damage
  - Most severe if nerve transected at its proximal portion  $\rightarrow$  frequently permanent
  - Avoided by staying above SMAS

- Abnormal sensation
  - Due to sensory nerve injury
  - Generally improves with time
  - Minimize by avoiding transection of multiple sensory nerve branches (e.g., orienting linear repairs on forehead vertically rather than horizontally)

## 8.14 SCAR IMPROVEMENT

### Overview

- Scars mature over at least **2 years**, but if not exhibiting favorable characteristics, may consider intervention after 60–90 days
- Manage expectations
  - Goal is to improve, not erase
- Result depends on
  - Size
  - Location
  - Patient’s predisposition for appropriate wound healing
- Favorable scars
  - Positioned along aesthetic subunit borders
  - Parallel with relaxed skin tension lines

### Nonsurgical modalities

- Watchful waiting
- Massage
  - Efficacy greatest in postsurgical scars
  - Often best for subtle imperfections
    - Mildly depressed scars
    - Mild webbing
    - Mild pin cushioning
- Pressure therapy
  - Allows natural scar maturation process to progress
    - Thins the dermis
    - Decreases edema
    - Decreases blood flow and oxygen
  - Loses efficacy after 6 months of treatment
- Topical scar therapies
  - Silicone sheeting and gel
    - Mechanism unclear
    - Side effects (SEs)
      - ◆ Skin maceration
      - ◆ Rash
  - Vitamin E
    - Efficacy not proven in clinical trials
    - Noted to cause allergic contact dermatitis
  - Steroids
    - Mechanism of action
      - ◆ Binding of nuclear steroid receptor
      - ◆ Decrease activity of fibroblasts and decreases collagen production
    - Clinical activity
      - ◆ Softens scars and  $\downarrow$  hypertrophy/pin cushioning
    - Group I most efficacious, but  $\uparrow$  risk of SEs

- Imiquimod
  - Mechanism of action
    - ◆ Stimulates IFN- $\alpha$   $\rightarrow$   $\downarrow$ TGF- $\beta$  (note:  $\uparrow$ TGF- $\beta$  levels are a/w keloid formation)
    - ◆ IFN- $\alpha$   $\rightarrow$   $\uparrow$ collagen breakdown
  - Clinical activity
    - ◆ Prevention of keloid recurrence after excision
    - ◆ Results of studies have been mixed
  - Cream is applied nightly for 8 weeks
- Intralesional therapies
  - Steroids
    - Primarily used for hypertrophic and keloidal scars
    - Mechanism of action and clinical activity: same as for topical steroids
    - Consider intraoperative injection if patient has a history of keloids
  - 5-FU
    - Primarily used for hypertrophic and keloidal scars
    - Mechanism of action
      - ◆ Blocks transforming growth factor (TGF)- $\beta$ 2 gene in fibroblasts  $\rightarrow$   $\downarrow$ collagen production
    - Clinical activity
      - ◆ Softens scars and decreases hypertrophy
    - Can be used in combination w/ steroids
- Lasers
  - Pulsed dye laser 585–595 nm
    - Laser of choice for red, hyperemic, pigmented, or hypertrophic scars and keloids
    - Patient phototype important as melanin competes for laser absorption. Must use lower energy densities in darker skin tones.
    - Mechanism of action
      - ◆ Keloids: promotes scar remodeling as a result of nonspecific heating of dermal collagen
      - ◆ Redness: destruction of dermal vessels
  - Nd:YAG – 1064 nm
    - Noted to improve pigmentation, vascularity, pliability and height of keloids, and hypertrophic scars
  - Resurfacing lasers
    - Mechanism of action
      - ◆ Dermal heating leads to scar remodeling
    - Types
      - ◆ Ablative (CO<sub>2</sub> – 10 600 nm; Erb:YAG – 2940 nm)
        - $\rightarrow$  Destroys stratum corneum and deeper structures
        - $\rightarrow$  Uses: recontouring atrophic scars  $\rightarrow$  reported equivalent cosmesis to dermabrasion w/ faster clinical recovery
      - ◆ Nonablative
        - $\rightarrow$  Preserves stratum corneum with destruction of deeper structures
- Radiotherapy
  - Reserved for scars that are unresponsive to other treatments
  - As monotherapy, radiotherapy is inadequate for treatment of keloids
  - Frequently combined with surgical resection

- Mechanism of action
  - Control of collagen synthesis by affecting fibroblast proliferation and inducing apoptosis
- Best results reported with 15–20 Gy over five to six sessions in early postoperative period, typically started 24–48 hours after surgery

## Surgical modalities

- Dermabrasion/electroabrasion
  - Dermabrasion
    - Mechanism of action: epidermis and papillary dermis are removed  $\rightarrow$  allows wound to reepithelialize from surrounding epithelium and underlying adnexa
    - Best performed ~6 to 8 weeks postoperatively
    - Rewounding during fibrillogenesis stimulates  $\uparrow$ epidermal cell migration into wound  $\rightarrow$  improved appearance of scar
    - Variants:
      - ◆ Wire brush
        - $\rightarrow$  Creates microscopic lacerations
        - $\rightarrow$  Less forgiving than diamond fraise
      - ◆ Diamond fraise with hand engine
        - $\rightarrow$  Should rotate in the direction of free margin
        - $\rightarrow$  Feathering used to avoid demarcation between treated and untreated regions
      - ◆ Dermasanding
        - $\rightarrow$  Manually performed with medium-grade drywall sanding screen
        - $\rightarrow$  No aerosolization of infectious particles or blood splatter
        - $\rightarrow$  Cosmetically not different from mechanical dermabrasion
    - SEs
      - ◆ Hyper/hypopigmentation
      - ◆ Milia formation
      - ◆ Persistent erythema
      - ◆ Paradoxical worsening of scars
    - Electroabrasion
      - ◆ Mechanism of action: controlled skin ablation w/ hyfrecator (low power)
      - ◆ Similar results to dermabrasion
      - ◆ Procedure and bleeding time less than dermabrasion
- Subcision
  - Utilized on depressed facial scars
  - A 20 gauge tribeveled hypodermic needle inserted in the skin and sharp edges are maneuvered to release fibrotic scar bands within dermis and subcutaneous tissue
- Scar excision procedures
  - Linear excision of scar
  - W plasty
    - Irregularization technique; typically followed by dermabrasion
  - Geometric broken line
    - Irregularization technique; incise connected random geometric figures (squares, rectangles, and triangles); typically followed by dermabrasion

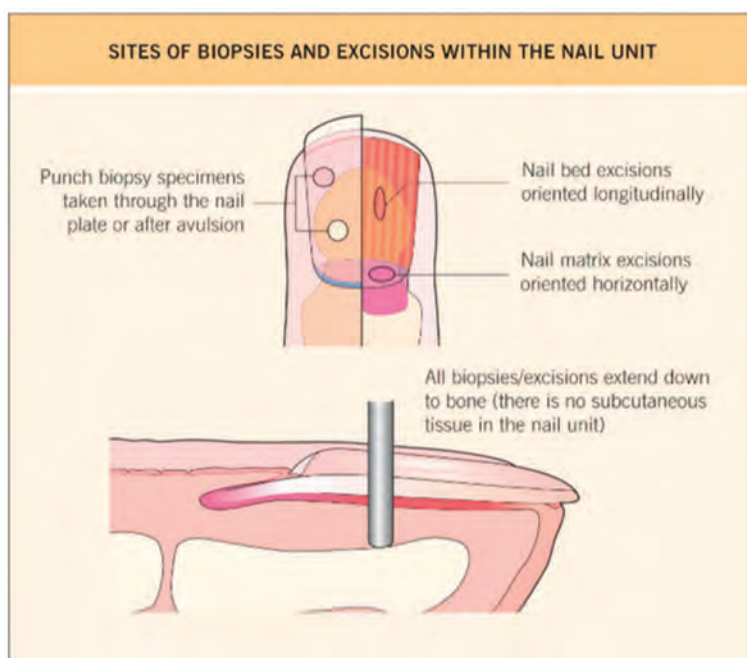


- Scar reorienting/lengthening techniques
  - V to Y
    - Can push (V-Y) or pull (Y-V) a free margin into place. Include figure: (Lee et al. Surgical revision. Dermatol Clin. 2005 Jan;23(1):141-50. Fig. 7)
    - Less dramatic lengthening than Z-plasty
  - Z-plasty
    - Used to lengthen scar or release contractions
    - Angle of the lateral arms relative to the central limb determines the amount of lengthening
    - The greater these angles are the more lengthening will occur, however the flaps become harder to transpose over one another
    - 30° lengthens by 25%
    - 45° lengthens by 50%
    - 60° lengthens by 75%

Include figure (Robinson, 2nd ed., Fig. 20-6)

## 8.15 NAIL SURGERY

- Nail avulsion: typically undertaken for treatment of onychomycosis, onychomadesis, nail biopsy, nail matrix ablation, or nail unit excision
  - Distal nail avulsion (most commonly used technique): entire nail is separated from distal nail bed to proximal nail fold
  - Proximal nail avulsion: less traumatic than distal nail avulsion; undertaken when there is **prominent subungual hyperkeratosis**
  - Partial nail avulsion: used when exact location of lesion in question is already known
- Nail biopsies (Fig. 8-26):
  - Nail bed:
    - **Longitudinal excision**; excision extends down to periosteum; +/- suturing of defect (not required if defect width  $\leq 3$  mm); **minimal risk of nail dystrophy**
  - Nail matrix:
    - **Horizontal excision**; make diagonal 5 mm incision from proximal nail fold (extending proximally on finger) to allow visualization of matrix → biopsy carried down to periosteum
    - Matrix biopsies have ↑**risk of nail dystrophy/thinning**; highest risk w/ proximal matrix biopsies and if >3 mm width
    - Most nail **melanomas arise from matrix** → matrix biopsy required → ↑risk of nail dystrophy
  - Lateral longitudinal nail biopsy:
    - Longitudinal excision used for lesions on lateral nail fold, proximal nail fold, or lateral portions of matrix/bed
    - Main risks = **spicule or cyst formation**
- Matricectomy
  - Removes nail matrix → inability to form a new nail
  - Indications: **ingrown nail/onychocryptosis (#1)** or onychomadesis
  - Typically only the part of the matrix causing problems needs to be removed
  - Excision of nail unit
    - En-bloc excision is typically undertaken for removal of malignant tissue, such as a subungual melanoma; aggressive procedure that may result in permanent stiffness at the joint, but may be preferable to amputation
    - Excision must be taken back to DIP tendon insertion to have reasonable chance of removing entire matrix



**Figure 8-26.** Sites and orientations of biopsies and excisions within the nail unit. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Phenol matricectomy
  - Mostly used for ingrown toenails
  - Phenol is applied three times with a cotton-tipped applicator for 2–3 minutes after nail avulsion
  - ECG monitoring is not necessary; some will neutralize the phenol with alcohol after application
- Excision and electrodesiccation of the nail matrix have been advocated by some authors as alternatives to phenol; limited data exist on its benefits and harms relative to other forms of nail matricectomy
- Subungual hematoma:
  - Trephination indicated if **hematoma >50% of nail**
  - May occur in combination w/ fractured distal phalanx → **X-rays recommended**

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# Cosmetic Dermatology

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## 9.1 LASERS

- LASER = Light Amplification by Stimulated Emission of Radiation ([Table 9-1](#))
- Lasers are characterized by the “3 C’s”
  - Coherence: light waves travel together in-phase in time and space
  - Collimation: light waves travel together in a parallel fashion
  - (mono)Chromatic: light waves are all the same wavelength
- Three different media exist (determine laser wavelength):
  - Gas: CO<sub>2</sub>, xenon chloride (excimer laser), krypton, argon, copper vapor, helium-neon
  - Liquid: rhodamine dye (PDL)
  - Solid: two classes exist
    - Crystal: alexandrite, Er-YAG, Nd-YAG, potassium titanyl phosphate (KTP), and Ruby
    - Semiconductor: diode
- **Selective photothermolysis**: using a laser to achieve selective destruction of the target structure(s); depends on three factors:
  - **Wavelength** must target the desired chromophore and reach an appropriate anatomic depth to destroy the desired target tissue
  - **Pulse duration should be  $\leq$  TRT** (thermal relaxation time)  $\rightarrow$  minimizes diffusion of heat and resultant “collateral damage” to surrounding tissues
  - **Fluence** must be high enough to damage target tissue, but not so high as to nonspecifically damage bystander tissue
- Four different types of laser wave forms:
  - Continuous: emit light continuously; low power (examples: CO<sub>2</sub> laser, and argon)
  - Pulsed: light is emitted periodically, with short pulse durations (millisecond [ms] range), and high power (examples: PDL, ruby, alexandrite, diode, Erbium:glass, and Erbium:YAG)
- Quality switched (Q-switched): variant of pulsed lasers with **extremely short pulse durations (nanosecond range)**; **extremely high power** (example: all QS lasers)
  - Lasers of choice for **pigmented lesions, tattoos, and drug deposits**, because target molecules are very small  $\rightarrow$  very short TRT (nanoseconds)
- Quasicontinuous: emits multiple rapid bursts of low-energy light  $\rightarrow$  simulates continuous wave lasers (examples: KTP and copper vapor)
- Treated skin will have at least one of the following four interactions with emitted laser light particles:
  - Reflection: 4–7% of light is reflected (“bounced away”) by skin surface, as a result of the difference in refractive index between air and stratum corneum; the remaining 93–96% of light enters skin and will subsequently interact in one of three following ways:
    - Scattering: light bounces off fibers within dermis/SQ  $\rightarrow$  **limits depth of penetration**
      - ◆  $\uparrow$  spot size  $\rightarrow$   $\downarrow$  scatter  $\rightarrow$   $\uparrow$  depth of penetration
    - Transmission: light passes straight through the tissue without interacting with anything  $\rightarrow$  lack of any effect
    - Absorption (desired effect): light is absorbed by its intended target  $\rightarrow$  tissue effects
- Epidermal damage is minimized via skin cooling (three commonly used methods):
  - **Precooling**: most aggressive and effective method (example: **cryogen (tetrafluoroethane) spray**)
    - Main side effect (SE) = **hyper/hypo-pigmentation**
  - **Parallel cooling**: only effective for pulses  $>5$  ms in duration (example: solid cold sapphire window pressed against skin)

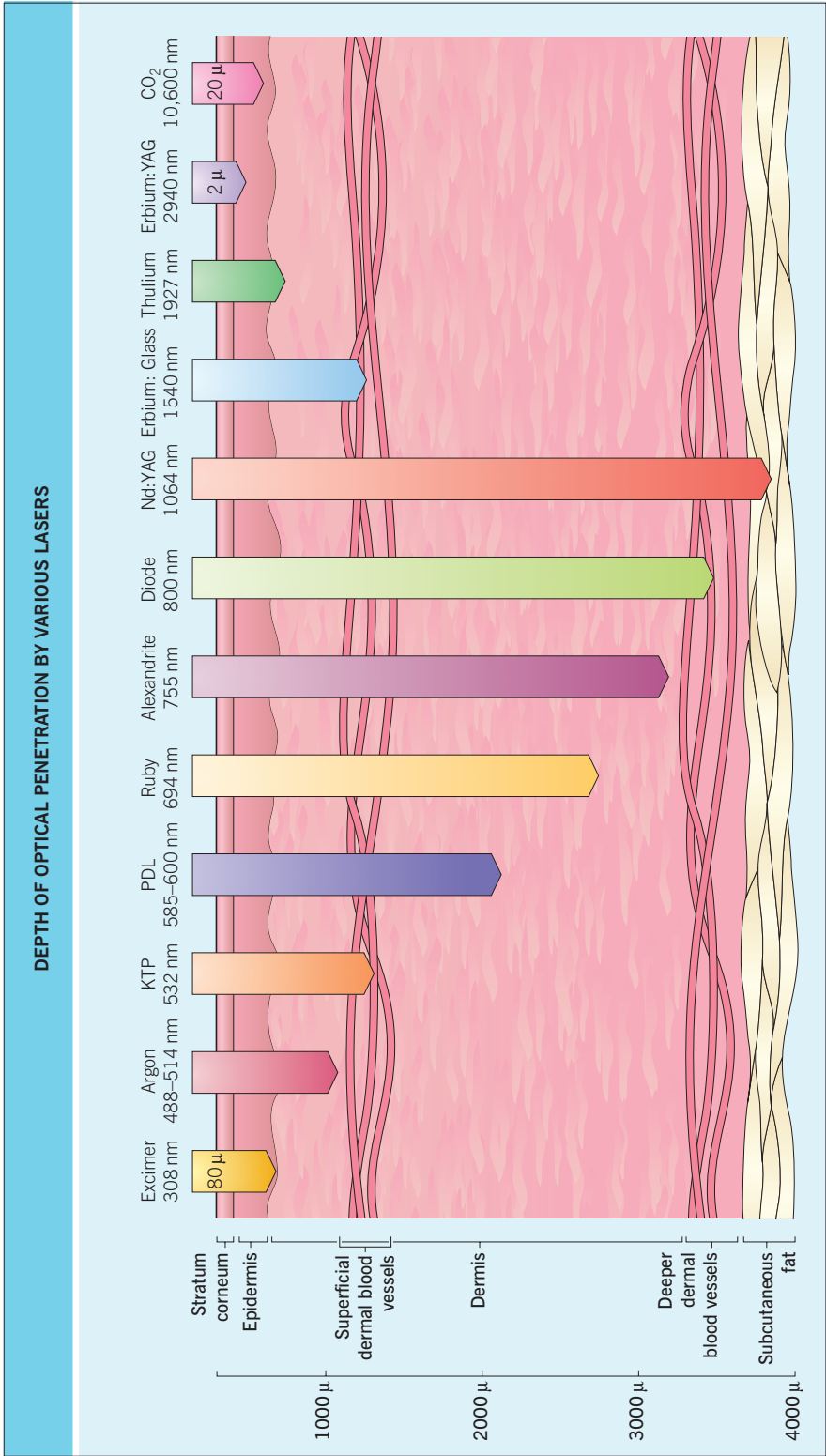
**Table 9-1.** Laser Terminology

Term	Definition	Unit	Comments
Energy	Fundamental unit of work	Joules (J)	—
Fluence	Energy delivered per cm <sup>2</sup>	J/cm <sup>2</sup>	↑fluence → ↑energy of treatment per unit area
Power	Rate of energy delivery	Watts (W) = J/s	—
Irradiance	Power delivered per cm <sup>2</sup>	W/cm <sup>2</sup>	—
Pulse width (pulse duration)	Duration of laser exposure (seconds)	Seconds (or fractions of seconds)	↑ pulse duration = longer exposure to the laser → ↑energy/heat delivered to tissue Ideally, pulse duration should be ≤TRT to prevent collateral damage to bystander tissues
Spot size	Diameter of the laser beam hitting the skin surface (mm)	mm	Larger spot size → ↓scatter → ↑depth of penetration
Wavelength	Length of a specific laser's light wave Four categories: <b>UV (10–400 nm)</b> <b>Visible (400–700 nm)</b> <b>Infrared (700 nm–1 mm)</b> <b>Radiofrequency/microwaves (&gt;1 mm)</b>	nm (most commonly)	<b>Longer wavelengths penetrate deeper</b> (rule holds true until 1300 nm, at which point penetration decreases as a result of water absorption) Most deeply penetrating wavelengths = 650–1200 nm Least penetrating wavelengths = far UV and far IR
Chromophore	Absorptive target tissue of laser	—	Major chromophores in skin (boards favorite): <b>melanin</b> , <b>hemoglobin</b> (oxyhemoglobin and deoxyhemoglobin), and <b>water</b> A laser/light source may target multiple chromophores to differing degrees
Thermal relaxation time (TRT)	The time required for heated tissue to dissipate 50% of its heat	Seconds (or fractions of seconds); proportional to the diameter of target squared	<b>TRT (seconds) is proportional to the square of the target's diameter</b> (in mm) Ideally, <b>pulse duration should be ≤TRT</b> If pulse duration > TRT → ↑undesired damage to surrounding tissues (Table 9-2)
Photomechanical effect	Sudden heating produces thermal expansion with acoustic and/or shock waves → waves produce cavitation (steam bubbles)	—	<b>Cavitation</b> is the <b>primary mechanism of vessel rupture w/ PDL</b> , and also is responsible for skin whitening during QS-laser treatment of tattoos

- Postcooling: used primarily to ↓ pain, erythema, and edema (example: ice packs and cold air)
- A variety of lasers exist, each with specific wavelengths, target chromophores, and depths of penetration (Fig. 9-1 and Fig. 9-2)
- Nonlaser energy sources
  - Intense pulsed light (IPL):
    - Xenon flashlamp (light source) emits noncollimated, noncoherent, and polychromatic light (broad wavelength range: 500–1200 nm)
    - A variety of filters are utilized to narrow down the range of wavelengths to target the same chromophores that lasers do
    - Less selective and less powerful than lasers
  - Radiofrequency (RF):
    - Electrodes deliver alternating electric current → locally heats tissue
    - Much less selective and less powerful than lasers and IPL, but does have some specificity for fat (hence, RF is used primarily for cellulite, and to a lesser extent, skin tightening)
- Blindness is rapid and painless
- Any laser/light source in UV range → lens damage, cataracts
  - Example: excimer laser (308 nm)
- Any laser/light source that targets melanin or hemoglobin (visible light and near-infrared wavelengths) → retinal damage (retina is highly pigmented); also damages uvea and iris
  - Examples: KTP (532 nm), PDL (585–600 nm), ruby (694 nm), IPL (various wavelengths), alexandrite (755 nm), diode (800 nm), and Nd:YAG (532 nm and 1064 nm)
  - Highest risk = near infrared and Q-switched lasers
- Any laser/light source that targets water (mid and far-infrared wavelengths) → corneal/scleral damage
  - Examples: Nd:YAG (1320 nm), Erbium:glass (1550 nm), Erbium:YAG (2940 nm), and CO<sub>2</sub> (10 600 nm)
- Fire hazard
  - Greatest fire risk with CO<sub>2</sub> and Erbium:YAG ablative and fractionated lasers
  - Risks: drapes, clothing, dry hair, and plastic tubes (endotracheal tubes, especially if oxygen is being administered)
  - Prevention: moisten hair near treatment field, ensure that any alcohol/acetone skin cleanser has fully dried before using laser, and reduce intraoperative O<sub>2</sub> concentration <40%
- Cutaneous burns: may occur with any laser or nonlaser energy source (IPL and RF); as a result of operator error

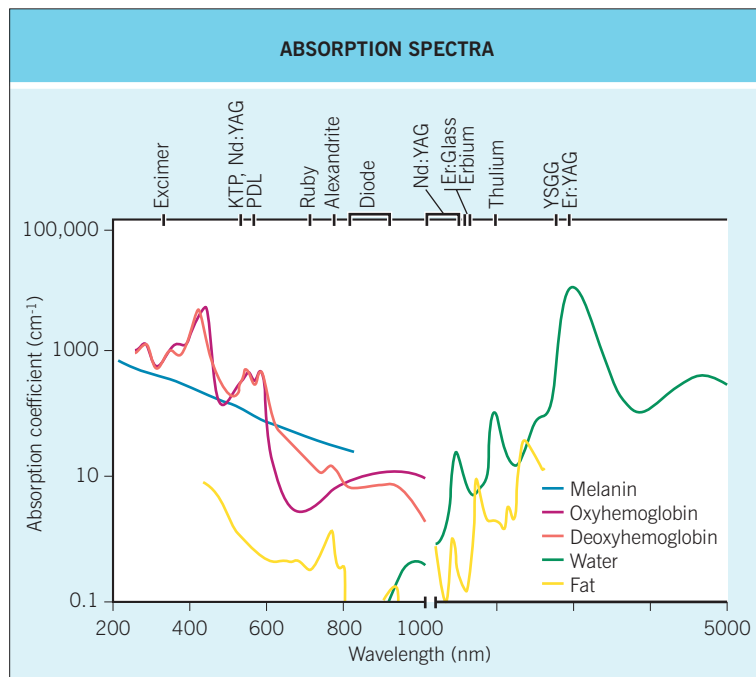
## Laser safety

- Four main concerns: blindness, fire hazards, cutaneous burns, and inhalation of biohazardous plume
- Blindness
  - Up to 7% of emitted laser light is reflected by the stratum corneum → reflected light can cause eye damage/blindness (may occur if even 1% of the beam is reflected into eye)



**Figure 9-1.** Depth of optical penetration by various lasers. It should be noted that the treatment depth can greatly exceed the optical penetration depth for ablative lasers. On the face, fat can be present at a depth of 2–3 mm. For example, the depth of optical penetration for CO<sub>2</sub> lasers is only ~20 microns, but fractional CO<sub>2</sub> lasers can vaporize nearly full-thickness microchannels through the dermis. KTP, potassium titanyl phosphate; Nd, neodymium; PDL, pulsed dye laser; YAG, yttrium aluminum garnet. (From Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier, 2012)





**Figure 9-2.** Absorption spectra. The heterogeneous absorption spectra of chromophores allow selective photothermolysis to work. Er, erbium; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet; PDL, pulsed dye laser; YSGG, yttrium scandium gallium garnet. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

**Table 9-2.** Thermal Relaxation Times of Chromophore

Chromophore	Diameter	Thermal Relaxation Times	Typical Pulse Duration
Tattoo ink particle	0.1 micrometer	10 nanoseconds	0.6–10 <b>nanoseconds</b> (requires Q-switched lasers)
Melanosome	0.5 micrometers	250 nanoseconds	10–100 <b>nanoseconds</b> (requires Q-switched lasers)
PWS vessels	30–100 micrometers	1–10 milliseconds	0.4–20 milliseconds
Terminal hair follicle	300 micrometers	100 milliseconds	3–100 milliseconds
Leg vein	1 millimeter	1 second	~ 0.1 seconds

(From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*, 3rd Ed. Elsevier. 2012)

- Inhalation of biohazardous plume
  - HPV viral particles have been detected in laser plumes → cases of laser-surgeons developing HPV-16-induced oral SCC related to inhalation
  - Prevention: **ventilation** and/or **smoke evacuator**; also recommend N95 mask

## Vascular lasers

- Commonly treated vascular lesions: blood vessels as a result of photoaging, redness associated with (a/w) rosacea, spider angiomas, Poikiloderma of Civatte, hemangiomas, vascular malformations, redness in striae, redness in scars, verruca vulgaris, and Kaposi sarcoma (less common)
- Utilize selective photothermolysis to damage blood vessels via coagulation of vessel contents → vessel collapse or destruction
- Target: hemoglobins (oxyhemoglobin > deoxyhemoglobin > methemoglobin)
  - Absorption peaks = 418, 542, and 577 nm
- Main SE = **purpura** (primarily PDL)
  - Other SEs **dyschromia** (↑risk in darker skinned patients), **blistering** (↑risk with shorter pulse widths, higher fluences, and skin of color)
- Skin cooling via **precooling** is critical → prevents epidermal damage
  - Also allows for greater patient comfort and allows physician to treat at higher, more efficacious fluences
- General anesthesia is recommended for larger pediatric lesions
- Site of eye damage: **retina**
- Consider HSV prophylaxis for perioral lesions, or larger facial malformations
- Desired treatment endpoints:
  - **PDL – purpura** (as a result of cavitation and vessel rupture)
    - Nonpurpuric regimens utilize pulse durations of 20 ms or higher → do not get cavitation or vessel rupture → do not get immediate purpura (but frequently get delayed purpura days later)
  - KTP, Nd:YAG – immediate disappearance of vessel
- Complex vascular lesions typically require several treatments
- Boards fodder:
  - **PDL** (585–600 nm) is the treatment of choice for **most vascular lesions** (PWS, telangiectasias, erythematous scars, and hemangiomas)

- IPL is the TOC for **Poikiloderma of Civatte** (treats both the vessels and dyschromia)
  - If IPL is not an option on the examination, PDL would be second best choice
- **Long-pulsed Nd:YAG (1064 nm)** is the laser of choice for most vascular ectasias on the lower leg (venulectasias, telangiectasias, and reticular veins), because it penetrates deeper than other vascular lasers
  - Diode (800 nm) would be the second best choice
- IPL or **long-pulsed PDL** (nonpurpuric) are the treatments of choice for **erythematotelangiectatic rosacea**

## Hair reduction lasers and light sources

- Common laser hair reduction uses: removal of unwanted hair, pseudofolliculitis barbae, hidradenitis suppurativa, and pilonidal cyst disease
- Laser hair reduction is based upon the principle of **selective photothermolysis**
- **Target: melanin** within hair shaft, ORS, and matrix
  - Absorption peaks: broad range (~300–1000 nm)
- Destruction of **bulge and bulbar stem cells** → improved hair removal
- Dark, thick terminal anagen hairs respond best
  - Thinner, lighter hair is hard to remove
  - **White hair is impossible to remove** (lacks target chromophore) → other epilation techniques recommended
- Adverse effects:
  - **PIH** (↑ in skin of color)
    - Recommendation: treat test spot and follow up in 1 to 2 weeks
  - Leukotrichia
  - Blistering/burning (↑ risk in skin of color) may → scarring
- Site of eye damage: **retina**
- Requires multiple treatment sessions, spaced 4 to 6 weeks apart; treatments often not permanent → goal is “reduction, rather than removal”
- Recommend shaving before treatment in order to shorten hairs → ↓ skin burns from hairs on skin surface
- **Do NOT fully remove hair shafts** by chemicals, waxing, plucking, or threading for at least 6 weeks before treatment (eliminates target chromophore)
- **Treatment endpoint = transient perifollicular edema**
- Use wavelength-specific eyewear to protect **retina**
- Use parallel cooling to protect the epidermis during treatment
- **Boards fodder:**
  - **Diode is most efficacious**; usually safe in skin of color (but not as safe as Nd:YAG)
  - **Nd:YAG (1064 nm) = safest hair removal laser in skin of color**, but slightly less effective (Table 9-3)

## Resurfacing lasers (Table 9-4)

- Common indications: rhytids, photoaging and actinic damage, acne scars, keloid, hypertrophic and burn scars, postsurgical scars, benign skin lesions (SKs/warts/syringomas), striae, and rhinophyma

**Table 9-3.** Laser/Visible Light Sources for Hair Removal

Laser	Wavelength	Skin Type	Comments
Alexandrite	755 nm	Skin types I–III	—
Diode	810 nm; 940 nm	Skin types I–III	Most effective
Nd:YAG	1064 nm	All skin types	Safest in skin of color
IPL	Varying filters	Unsafe in skin types IV–VI	—

- **Target: water**
  - Absorption peaks: 1450, 1950, and 3000 nm
- May be ablative or nonablative
  - Ablative lasers function by removing skin via **vaporization of target tissue**
  - Nonablative lasers work via subtle **thermal effects on dermis** → stimulates a wound healing response
- May be fractionated or nonfractionated
  - Fractionated: creates thousands of microscopic thermal zones of injury (MTZ) → stimulates turnover/remodeling of epidermis and dermis
    - Advantages: ↓ **downtime** and ↓ **duration of erythema** compared with nonfractionated resurfacing
    - Disadvantages: less efficacious; requires more treatment sessions
- Site of eye damage: **cornea, sclera** (burns)
- Consider HSV/fungal/bacterial prophylaxis
- Adverse effects:
  - Erythema (often persists for months)
  - Hyperpigmentation
  - Relative hypopigmentation (↑ risk if deeper injury; may arise months after treatment)
  - Milia
  - Secondary infections
    - HSV: **highest risk in first week**
    - Bacteria (*S. aureus*, *Pseudomonas*)
  - Scarring

## Tattoo removal lasers (Table 9-5)

- Tattoo pigments are very small in diameter → very short TRT (nanoseconds) → **QS-lasers are required**
- **Immediate tattoo whitening** (desired endpoint) is a result of cavitation
- Amateur tattoos and black tattoos are the most responsive to treatment (usually <5 treatment sessions)
- Professional tattoos and multicolored tattoos most difficult to treat (>10 treatment sessions)
- Boards fodder:
  - Mnemonic: “The 3 B’s (black, brown blue tattoos) **RAN** away when they saw the 3 **lasers**” → all 3 colors are treated with Ruby, Alexandrite, or Nd:YAG
  - Mnemonic: “If you have a Yellow, White, Red, or Violet tattoo, You Will Return Visit for 2 or more treatments with frequency-(2)**doubled Nd:YAG**”
  - Only ruby and alexandrite treat **green** tattoos
  - Red tattoos (cinnabar [mercuric sulfide]) → most likely to cause **allergic reactions**

**Table 9-4.** Resurfacing Lasers

Laser	Wavelength	Comments
<b>Ablative</b>		
Erbium:yttrium scandium gallium garnet (Er:YSGG)	2790 nm	Less thermal injury → poor coagulation, ↑bleeding, and ↓collagen retraction
Erbium:yttrium aluminum garnet (Er:YAG)	2940 nm	Less thermal injury → poor coagulation, ↑bleeding, and ↓collagen retraction Targets the 3000 nm absorption peak of water more effectively than CO <sub>2</sub> laser Advantages compared with CO <sub>2</sub> laser: ↓recovery time, ↓PIH, and erythema resolves more quickly
Carbon dioxide (CO <sub>2</sub> )	10,600 nm	More thermal injury → good coagulation, minimal to no bleeding, and ↑collagen retraction Depth of ablation is increased by performing more passes
<b>Nonablative</b>		
Vascular lasers (PDL)	585–600 nm	PDL +/- amino-levulinic acid: may also help treat coexisting AKs and actinic cheilitis
Infrared lasers	Nd:YAG (1064, 1320 nm) Diode (1450, 1470 nm) Er:glass (1540 nm)	All achieve mild dermal tightening, but do not help with epidermal sun damage Diode is more effective at treating acne scarring than others
IPL	515–1200 nm	Leads to mild dermal tightening and also treats epidermal photodamage
Radiofrequency	NA	Electrical current heats dermis → mild skin tightening

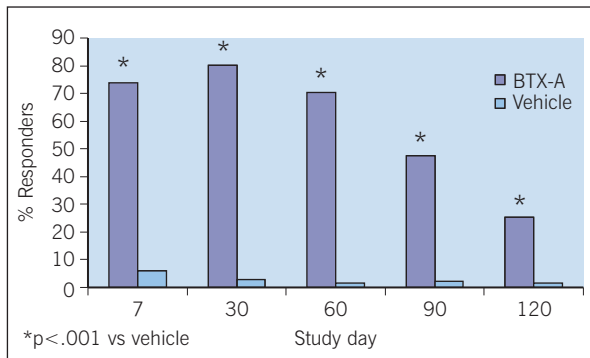
**Table 9-5.** Tattoo Removal Lasers

Tattoo Color	Pigment	Laser (All are Q-switched)	Wavelength (nm)
Black	Iron oxide, carbon, india ink, lead, and gunpowder	<b>Ruby</b> Alexandrite <b>Nd:YAG</b>	694 755 1064
Blue	Cobalt	Ruby Alexandrite Nd:YAG	694 755 1064
Brown	Ochre	Ruby Alexandrite Nd:YAG (frequency-doubled) Nd:YAG	694 755 532 1064
Green	Chromium oxide, malachite green	Ruby <b>Alexandrite</b>	694 755
Yellow	Cadmium sulfide, ochre	<b>Nd:YAG (frequency-doubled)</b>	<b>532</b>
White	Titanium dioxide, zinc oxide	<b>Nd:YAG (frequency-doubled)</b>	<b>532</b>
Red	<b>Mercuric Sulfide (cinnabar)</b> , azo dyes, cadmium selenide, and sienna	<b>Nd:YAG (frequency-doubled)</b>	<b>532</b>
Violet	Manganese violet	<b>Nd:YAG (frequency-doubled)</b>	<b>532</b>

- Laser treatment in patient allergic to tattoo dye → possible **anaphylaxis**
- **White** tattoos may undergo **immediate paradoxical darkening** (turns black or blue) with laser because of reduction of  $Ti^{4+} \rightarrow Ti^{3+}$
- **Pink, flesh-toned, or light red** tattoos (classically, permanent lip liner) may undergo **immediate paradoxical darkening** (turns brown-black) with laser because of reduction of **ferric oxide** ( $Fe^{3+}$ ) → **ferrous oxide** ( $Fe^{2+}$ )
- Traumatic tattoos from gunpowder/fireworks → may explode with laser
- **Pigmented lesions** (lentigines, ephelides, or nevus of Ota) are treated with the same lasers as black tattoos ("RAN" lasers)
  - **Ruby** is classically the laser of choice for nevus of Ota/Ito
- Minocycline hyperpigmentation → treated with the same lasers as black tattoos ("RAN" lasers)

## 9.2 BOTULINUM TOXIN

- Botulinum toxin is a neurotoxin derived from the anaerobic gram(+) bacilli *Clostridium botulinum*
- There are eight subtypes of botulinum toxin (A-H) (Table 9-6), but only two (types A and B) are in clinical use
- Mechanism: Botulinum toxin inhibits the function of nerve terminals through **presynaptic blockade of SNARE complex** → **prevents acetylcholine (ACh) release** → chemical denervation of muscle → over time, the muscle undergoes atrophy (Fig. 9-3)
- FDA-approved for the temporary improvement in the appearance of glabellar lines and the lateral canthi lines, as well as axillary hyperhidrosis
  - Effect typically lasts about 3 months, and may take up to 1 week to demonstrate full effect
  - Remember, rhytides are perpendicular to muscle fibers



**Figure 9-3.** Response to BoNT peaked at day 30 and was significantly greater than the placebo (vehicle) at every follow-up visit. (Data from Carruthers JA, Carruthers JDA, Lowe NJ, et al. One year, randomized, multicenter, two period study of the safety and efficacy of repeated treatments with botulinum toxin type A in patients with glabellar lines. *J Clin Res* 2004;7:1–20)

**Table 9-6.** Botulinum Toxin Subforms and Site of Action

Botulinum Toxin Subtype	Site of Action in SNARE Complex of Proteins
A	Snap-25
B	SynaptoBrevin
C	Snap-25, Syntaxin
D	Synaptobrevin
E	Snap-25
F	Synaptobrevin
G	Synaptobrevin
H	Synaptobrevin

- Three forms of botulinum toxin type A and one form of botulinum toxin B currently marketed in the USA ([Table 9-7](#))
- Typical botulinum toxin injection points are shown in [Figure 9-4](#) and injection doses are shown in [Table 9-8](#)
- Pregnancy category C; **contraindicated with neuromuscular disorders** (e.g., myasthenia gravis, Lambert-Eaton syndrome, or amyopathic lateral sclerosis)
- **Do not give with aminoglycoside antibiotics** (e.g., gentamycin) → ↑ neuromodulatory effect
- One of the possible SEs of botulinum toxin injections is **eyelid ptosis** (do NOT inject lateral to mid-pupillary line); **prescription: α-agonist (apraclonidine 0.5%, naphazoline, or phenylephrine 2.5%)** → **stimulates Muller's muscle** → improves eyelid ptosis
  - Other SEs (depend on site injected): blurred/double vision, mouth droop (depressor labii inferioris), difficulty speaking (orbicularis oris), cheek drooping (zygomaticus – be careful when injecting crow's feet!), swallowing difficulties (platysma), and bruising (arnica and bromelain can help with bruising)

## 9.3 DERMAL FILLERS

- Dermal fillers are used to provide volume augmentation → more youthful appearance of face ([Table 9-9](#))
- Filler components have changed over time and the use of fillers has expanded rapidly with the development of hyaluronic acid (HA)-based fillers
  - Bovine and human collagen fillers no longer available

**Table 9-7.** Different Forms of Botulinum Toxin Type A in the United States

	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	RimabotulinumtoxinB
Brand name	Botox®	Dysport®	Xeomin®	Myobloc®
Molecular composition	150 kDa neurotoxin with complexing proteins	150 kDa neurotoxin with complexing proteins	150 kDa neurotoxin	150 kDa neurotoxin
Molecular weight	900 kDa	500–900 kDa	150 kDa	700 kDa
Recommended dose for glabellar lines	20 U	50 U	20 U	20 U
Target protein	Snap-25	Snap-25	Snap-25	<b>Synaptobrevin</b>
Storage before/after reconstitution	2–8°C/2–8°C	2–8°C/2–8°C	<25°C/2–8°C	2–8°C/2–8°C

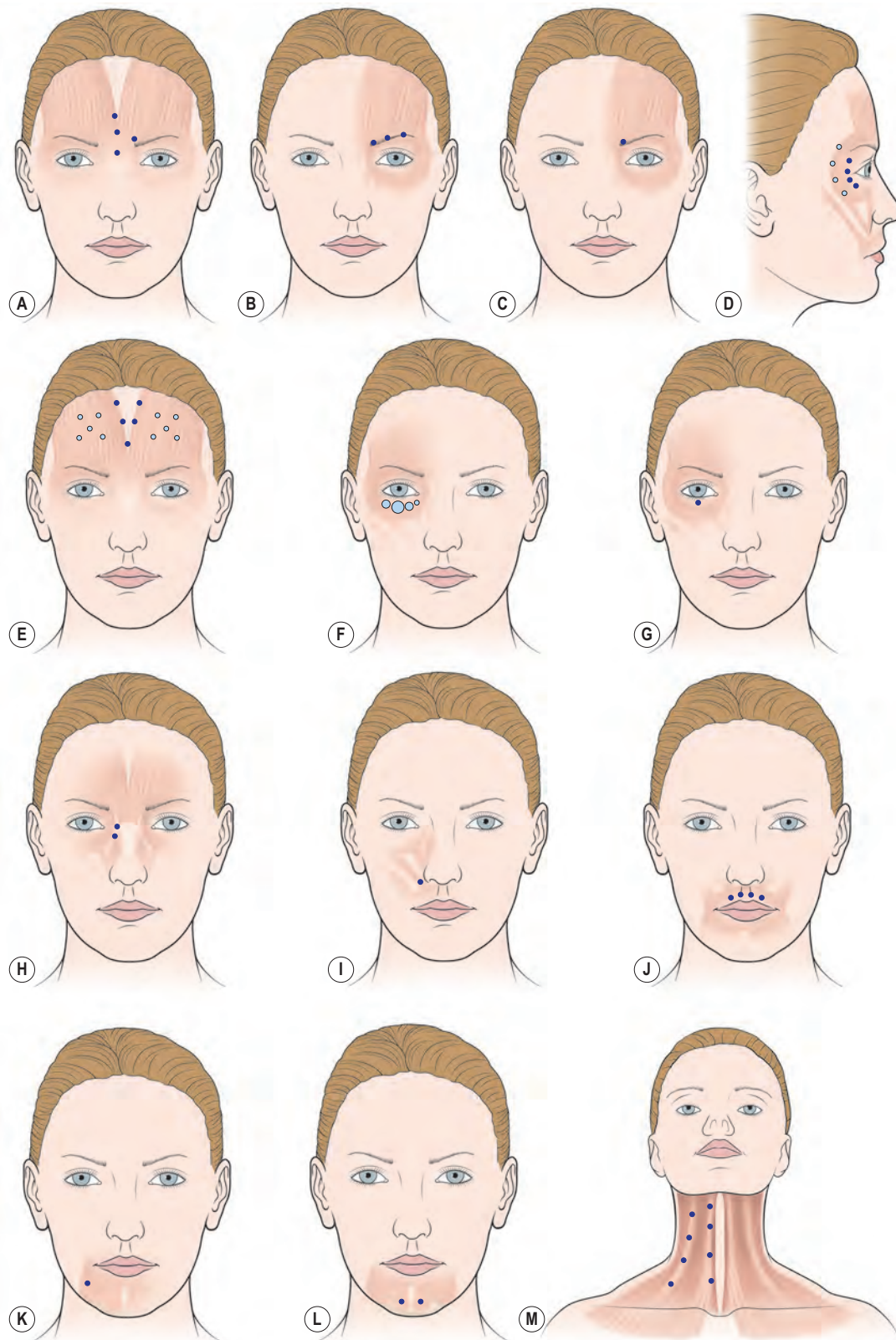
(Adapted from Frevert J. *Pharmaceutical, Biological, and Clinical Properties of Botulinum Neurotoxin Type A Products*. Drugs R D. 2015)

**Table 9-8.** Recommended Injection Dosing of Botulinum Toxin A

Area of Injections	OnabotulinumtoxinA/ IncobotulinumtoxinA (Units)	AbobotulinumtoxinA (Speywood Units)
Forehead lines (frontalis)	6–15	20–60
Glabellar lines (procerus and corrugator supercilii)	10–40	50
Lateral canthi lines (orbicularis oculi)	10–30	30–60
Bunny lines (nasalis)	4–8	10–20
Nasal tip droop	2–4	10
Lower eyelid	2	5
Drooping mouth corners/marionette lines (depressor anguli oris)	4–6	10–20
Dimpled chin (mentalis)	4–10	10–20
Gingival smile/"Gummy" smile (levator labii superioris alaeque nasi)	4–10	5–15
Platysmal bands	2–12 per band	5–30 (maximum of 50 per side)

(Adapted from Frevert J. *Pharmaceutical, Biological, and Clinical Properties of Botulinum Neurotoxin Type A Products*. Drugs R D. 2015)





**Figure 9-4.** The total face approach: injection sites to treat the glabellar region (A), eyebrows (B), mephisto (C), lateral canthal lines (D), forehead (E), lower eyelid (F), open eye (G), bunny lines (H), gummy smile (I), upper and lower lip (J), marionette lines (K), mentalis (L), and platysma (M). Blue dots, intramuscular injections of 1–2 U depending on the clinical situation and gender. Light blue circles, intradermal injections of 0.5–1 U.

**Table 9-9.** Dermal Fillers: Comparison of Fillers Currently Utilized in the USA

Filler Trade Name (®,™)	Source	Material	Duration of Effect	Advantages	Disadvantages	Use in Lips	Approved by the FDA	Volume Filler
Zyderm,* Zyplast*	Bovine	Collagen	2–4 months	Natural appearance, little swelling, and less painful to inject	Bovine, requires two skin tests, and short-lived	Yes	Yes	No
Cosmoderm,* Cosmoplast*	Human	Collagen	2–4 months	Natural appearance, little swelling, less painful to inject, and no skin test	Short-lived	Yes	Yes	No
Restylane fine lines	Bacteria-derived	Hyaluronic acid (smaller particle size)	4–6 months	No skin testing, effective for vertical lip lines	Short-lived	Yes	No	Yes
Restylane/ Restylane-L*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, relatively long-lasting, and versatile	Lip swelling, painful to inject without lidocaine	Yes	Yes	No
Perlane/ Perlane-L*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, relatively long-lasting	Lip swelling, painful to inject without lidocaine	Yes	Yes	Yes
Hylaform	Rooster comb	Hyaluronic acid	3–4 months	No skin testing, less lip swelling, and versatile	Short-lived, painful to inject <sup>†</sup>	Yes	Yes	No
Hylaform plus	Rooster comb	Hyaluronic acid (larger particle size)	4 months	No skin testing, less swelling	Short-lived, painful to inject <sup>†</sup>	Yes	Yes	Yes
Belotero balance	Bacteria-derived	Hyaluronic acid	6 months	No skin testing, excellent for treating fine and superficial rhytides	Cannot treat deep rhytides, painful to inject <sup>†</sup>	No	Yes	No
Juvéderm/ Juvéderm XC*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing	Painful to inject if without lidocaine	Yes	Yes	Yes
Juvéderm Ultra/Juvéderm Ultra XC*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, less lip swelling, and versatile	Painful to inject if without lidocaine	Yes	Yes	Yes
Juvéderm Ultra Plus/Juvéderm Ultra Plus XC*	Bacteria-derived	Hyaluronic acid (double cross-linked)	6–12 months	No skin testing, less lip swelling, and versatile	Painful to inject if without lidocaine	Yes	Yes	Yes
Prevelle silk*	Bacteria-derived	Hyaluronic acid	4–8 months	No skin testing	Short-lived, less painful to inject	Yes	Yes	No
Artefill	Synthetic	Bovine collagen and polymethyl-methacrylate beads (PMMA)	Permanent	Long-lasting, permanent	Skin testing (contains collagen), problematic injecting lips; permanent, including SEs (e.g., formation of nodules and granulomas)	No	Yes	Yes
Sculptra	Synthetic	Poly-L-Lactic acid	>1 year	Long-lasting, good volume filler	Tricky to inject, suspension preparation requires hours to days, multiple sessions required for correction, and occasionally formation of long-lasting palpable, but not visible, papules <sup>‡</sup>	No	Yes	Yes

Continued

**Table 9-9.** Dermal Fillers: Comparison of Fillers Currently Utilized in the USA—cont'd

Filler Trade Name (®,™)	Source	Material	Duration of Effect	Advantages	Disadvantages	Use in Lips	Approved by the FDA	Volume Filler
Radiesse	Synthetic	Calcium hydroxylapatite	>1 year	Long-lasting, good volume filler, and an equivalent volume appears to produce greater correction than the same volume of hyaluronic acid	Problematic injecting lips, painful to inject unless premixed with lidocaine	No	Yes	Yes
Silicone	Synthetic	Polydimethylsiloxane	Permanent	Versatile, permanent	Permanent, difficult injection technique (microdroplets), need multiple sessions for correction, and formation of permanent nodules	Yes	Yes (but not for esthetic indication)	Yes
SoftForm	Synthetic	Expanded polytetrafluoroethylene	Permanent	Permanent	Permanent, not widely used, and difficult to place	Yes	Yes	Yes
Gore-Tex subcutaneous augmentation material	Synthetic	Expanded polytetrafluoroethylene	Permanent	Permanent	Permanent, not widely used, and difficult to place	Yes	Yes	Yes
Autologous fat	Human	Fat	Permanent (in some patients)	Good for large areas of volume loss, permanent (in some patients)	Less predictable effects, permanence technique-dependent, and requires more instrumentation	Yes	Not applicable to autologous tissue	Yes
Fascian	Human (allograft)	Fascia	Months to years	Duration	Not widely used, difficult to place	Yes	Yes	Yes

FDA, Food and Drug Administration  
 \*Contains lidocaine.  
 †Pain of injection reduced by addition of lidocaine.  
 ‡Reduced to 1% to 2% by using larger volumes for dilution  
 (Adapted from Wesley N, Dover J. The filler revolution: a six year retrospective. *Drugs Dermatol* 2009;8:903–907)

- Complications (may occur with all fillers):
  - Ecchymoses
    - Avoid platelet inhibitors and vitamin E for 10 to 14 days before procedure
  - Nodules as a result foreign body granulomas
    - HA-fillers → “blue nodules” as a result of Tyndall effect (Fig. 9-5)
    - Prescription: IL-steroids; inject hyaluronidase for HA fillers
  - Painful blanching or cutaneous necrosis from occlusion of artery
    - Highest risk in glabellar region
    - Prescription (blanching): warm compresses and topical nitroglycerin; inject hyaluronidase for HA fillers
    - Prescription (necrosis): wound care
  - Blindness from occlusion of supratrochlear and supraorbital arteries can lead to occlusion of the central retinal artery
    - Highest risk in glabellar region
  - Anaphylaxis (rare)
    - Highest risk with bovine collagen (Zyderm, Zyplast; all currently off the market) → must



**Figure 9-5.** Granulomatous reaction on the right side of the upper lip 2 months after the injection of hyaluronic acid (arrows indicate swollen areas of the upper lip). (From Requena L, Requena C, Christensen L, et al. *J Am Acad Dermatol* 2011 Jan;64(1):1-34;quiz 35-6. doi: 10.1016/j.jaad.2010.02.064)

**Table 9-10.** Hyaluronic Acid (HA) Fillers

Filler	Juvaderm® Ultra	Juvaderm® Ultra Plus	Belotero®	Perlane®	Restylene®
Indication	Moderate to severe facial wrinkles and folds	Moderate to severe facial wrinkles and folds	Moderate to severe facial wrinkles and folds	Moderate to severe facial wrinkles and folds	Moderate to severe facial wrinkles and folds
HA Concentration (mg/mL)	24	24	22.5	20	20
Degree of cross-linking (%)	~6	~8	Variable	<2	<2
G'	Lowest			Highest	
Duration	9–12 months	12 months	<6 months	<6 months	< 6 months

(Adapted from Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. J Cosmet Dermatol 2009;8: 301–307 and Edsman K, Nord LI, Ohrlund A, et al. Gel properties of hyaluronic acid dermal fillers. Dermatol Surg 2012;38:1170–1179)

- perform **two skin tests before treatment** with bovine collagen
  - Very low risk with current fillers
- Prophylaxis against HSV may be indicated
- **Non-HA fillers of significance**
  - Polymethacrylate (ArteFill®): permanent filler for deep wrinkles
    - Polymethacrylate suspended in bovine collagen – thus skin testing required 30 days before procedure
    - Deep dermal injection
  - Calcium hydroxyapatite (Radiesse®): used in deep wrinkles and HIV lipoatrophy, hand rejuvenation, etc.
    - 9–18 month duration
    - **Radio-opaque** – seen on imaging
  - Poly-L-lactic acid (Sculptra®): used in **HIV lipoatrophy**, as well as deep wrinkles
    - 18–24 month duration
    - **“Rule of 5’s”** for massage of product – 5 minutes × 5 times/day × 5 days
    - Important to inject deep or else → papules/nodules
    - Idiopathic immunologic responses may occur immediately or up to 1 year after injection
- Differences between various HA fillers (Table 9-10) is as a result of the following:
  - **Concentration**: refers to the concentration of HA and includes both the free and cross-linked HA
    - Free HA does not contribute to the strength of the filler, only cross-linked HA does
  - **Degree of cross-linking**: refers to the % of the HA that is engaged in cross-links, including incomplete and complete cross-links
    - Natural HA is degraded within days; cross-linking of HA fillers results in macromolecules that are resistant to degradation
    - ↑cross-linking → ↑durability of HA fillers
  - **G'**: represents the elastic modulus of the filler in response to shear forces
    - ↑G' → ↑resistance to movement, ↓spread after placement, ↑volume support after injection
  - **Viscosity**: rates the flow of the filler
    - ↑viscosity → more force required to push it through a syringe

- **Boards fodder**: know the histologic features of the various fillers (see Dermatopathology chapter) and their reactions

## 9.4 LIPOSUCTION AND FAT REDUCTION

- Tumescence technique allows liposuction to be performed under **local anesthesia** → ↓ risk of major SEs (e.g., bleeding, bowel perforation)
- Liposuction involves the targeted removal of fat whereas many other methods rely on targeted destruction of the fat (Table 9-11)

## 9.5 SCLEROTHERAPY

- Superficial telangiectatic, reticular, and varicose veins of the lower legs constitutes a common cosmetic problem for patients
- Risk factors: genetic predisposition, hormones (estrogen and progesterone), obesity, and pregnancy
- Lower extremities have superficial and deep venous systems
  - Most important veins of the superficial venous system = **small and great saphenous veins**
    - These veins are typically the most cosmetically disturbing
    - Superficial varicosities located on the medial thigh → suggests greater saphenous insufficiency
  - Most important veins of the deep venous system = **femoral and popliteal veins**
- Myriad modalities are employed to treat cosmetically undesirable leg veins: sclerotherapy (Table 9-12), ambulatory phlebectomy, endovenous radiofrequency ablation, and laser ablation (Nd:YAG (long pulsed 1064 nm), IPL, and PDL); only sclerotherapy will be discussed further
  - Postprocedural compression stockings required for all forms of treatment
- Sclerotherapy is the treatment of choice for telangiectasias and reticular veins
  - Foaming may allow for treatment of larger varicose veins and perforating veins



**Table 9-11.** Fat Reduction Techniques

Technique	Mechanism of Action	Advantages	Side Effects	Notes
Cryolipolysis	Cold-induced apoptosis of adipose cells	Minimally invasive	Numbness and bruising Paradoxical adipocyte hyperplasia	After application of cold stimulus, the treatment area is massaged → this can be the most painful part for the patient
Deoxycholic acid injections	Degradation of adipose cells (adipocytolysis)	Minimally invasive	Erythema, bruising, edema, pain, numbness	<b>Deoxycholic acid</b> (ATX-101) was FDA approved in 2015 for treatment of <b>submental fat contouring</b>
Radiofrequency devices	Heat-induced apoptosis of adipose cells	Minimally invasive	Redness and edema May induce focal atrophy	Need multiple (6 or greater) sessions of treatment
Tumescent liposuction	Direct removal of subcutaneous adipose	Performed under local anesthesia → <b>↓major complications (bowel perforation and ↓bleeding)</b> Local vasoconstriction from tumescent anesthesia → ↓blood loss Does not require general anesthesia (vs conventional liposuction)	<b>Breast enlargement</b> (temporary) Abdominal pain Transient abdominal distention Infection/hematoma/ seroma Skin puckers/lumpiness Panniculitis Compartment syndrome Lidocaine toxicity	With tumescent method, <b>lidocaine limit is 55 mg/kg</b> (concentration = 0.05%–0.1%) Limit fat removal to 4500–5000 mL – done visa cannula autologous fat transfer – fat harvested from patient (via liposuction or specifically for the procedure; usually from abdomen/thighs/buttocks) and injected into deep wrinkles or hands
Mesotherapy injections	Degradation of adipose cells using various pharmacologic, plant-based and vitamin-derived ingredients	Minimally invasive	Infections, panniculitis, scarring	Not FDA regulated and may be ineffective and unsafe; thus far deoxycholic acid appears to be the only safe agent

**Table 9-12.** Important Characteristics of Sclerosing Solutions

Sclerosing Solution (Brand Name)	Class	Allergenicity	Risks	FDA Approval	Dose Limitation
Hypertonic saline [11.7%–23.4%]	Hyperosmotic	None	Pain* and cramping <b>Necrosis of skin</b> Hyperpigmentation	Yes, as abortifacient [18%–30%]	6–10 mL
Hypertonic saline [10%] and dextrose [25%] (Sclerodex®)	Hyperosmotic	Low (due only to added phenethyl alcohol)	Pain* (much less than with hypertonic saline alone)	No (sold in Canada)	10 mL of undiluted solution
Sodium tetradecyl sulfate (Sotradecol® (USA), Fibro vein®, Thromboject®)	Detergent	Very rare anaphylaxis	Pain* with perivascular injection Necrosis of skin (with higher concentrations) <b>Hyperpigmentation</b>	Yes	10 mL of 3%
Polidocanol (Asclera® (USA), Asklerol®, Aethoxysklerol®, Aetoxisclerol®, and Sclerovein®)	Detergent	Very rare anaphylaxis	Lowest risk of pain Necrosis usually from arteriole injection Hyperpigmentation (with higher concentrations) <b>Disulfiram-like reaction</b>	Yes	5 mL of 3% (depends on body weight, see ref. 5)
Sodium morrhuate (Scleromate®)	Detergent	<b>Anaphylaxis</b> , highest risk	Pain* Necrosis of skin Hyperpigmentation	Yes	10 mL
Ethanolamine oleate	Detergent	<b>Urticaria</b> , anaphylaxis	Pain* Necrosis of skin Hyperpigmentation Viscous, difficult to inject <b>Acute renal failure</b> <b>Hemolytic reactions</b>	Yes (used primarily for esophageal varices)	10 mL
Polyiodide iodide (Variglobin®, Variglobin®, and Sclerodine®)	Chemical irritant	Anaphylaxis, Iodine hypersensitivity reactions	Pain* Necrosis of skin Dark brown color makes intravascular placement more difficult to confirm	No	5 mL of 3%
Glycerin [72%] with chromium potassium alum [8%] (Chromex®, Scleremo®); glycerin [72%] diluted 2:1 with 1% lidocaine, with or without epinephrine)	Chemical irritant (plain glycerin may be an osmotic agent as well)	<b>Very rare anaphylaxis</b> (none for glycerin alone)	Pain* and cramping Low risk of hyperpigmentation Viscous, difficult to inject Hematuria with injections >10 mL	Yes (for treatment of acute intracerebral edema and acute angle glaucoma)	10 mL

Sclerosing agents are classified into three groups: hyperosmotic agents, detergents and chemical irritants.

\*Includes burning.

(From Bologna JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- There are three categories of sclerosing solutions, each with different mechanisms:
  - **Hyperosmotic agents:** stimulate endothelial damage via dehydration (most common = **hypertonic saline** +/- dextrose)
  - **Chemical irritants:** injure endothelial cells via corrosive action (most common = **glycerin**)
  - **Detergents:** induce vascular injury by altering the surface tension around endothelial cells (most common = **sodium tetradecyl sulfate (STS)**, **polidocanol**, sodium morrhuate, and ethanolamine oleate)
    - Sodium morrhuate and ethanolamine oleate can produce **severe necrosis** with extravasation and harbor a risk for allergic reactions → not recommended for routine sclerotherapy
- **Foaming** of sclerosing agents, ideally in a ratio of 1:4 (liquid air), is advantageous as it can ↓number of needed treatments, ↑efficacy when treating larger veins, and can be applied over a longer segment of a given vein
- Contraindications to sclerotherapy:
  - Allergy to sclerosants
  - DVT
  - Advanced arterial occlusive disease
  - Symptomatic patent foramen ovale (contraindication to foam sclerosant)
- **Complications:**
  - Urticaria (very common; rx: topical steroids or antihistamines; **highest risk of generalized urticaria with ethanolamine oleate**)
  - PIH (as a result of extravascular hemosiderin; Treatment: Q-switched lasers)
  - Telangiectatic matting (↓risk by using appropriate volume and concentration, and using low pressure when injecting; **highest risk with detergents and lowest with glycerin**)
  - Pain – worse with **hypertonic saline**
  - Swelling – important to use **graduated compression stockings postprocedure**)
  - Ulceration/cutaneous necrosis – **highest risk on dorsal foot and ankle**
  - Systemic allergic reaction – anaphylaxis (**highest with sodium morrhuate and lowest with polidocanol and glycerin**)
  - Inadvertent injection of an artery (most common sites of arterial injection: **posterior medial malleolus [posterior tibial artery; superficial injections]** and **popliteal fossa [deep injections]**)

## 9.6 COSMECEUTICALS AND NUTRACEUTICALS

- The term “cosmeceuticals” is derived as a blend of cosmetics and pharmaceuticals

- Cosmeceutical ingredients and scientific data showing evidence of one, some, or all of the following skin benefits are shown in [Table 9-13](#)

## 9.7 HAIR TRANSPLANTATION

- Male pattern baldness is typically classified along the Hamilton-Norwood system
- Female pattern hair loss has been graded along the Ludwig and Olsen patterns
- Medical options are available and discussed elsewhere in the book
- Surgical intervention involves hair transplantation ([Table 9-14](#))
  - Based on theory of **donor dominance** (transplanted hair retains characteristic of where it was taken from)
  - Grafts harvested from “safe zone” in **occipital scalp** (unaffected by AGA)
  - Usually greater than 25 follicular units/cm<sup>2</sup> for transplant to look natural
  - Two methods to harvest grafts ([Table 9-15](#)):
    - Strip (elliptical) excision – cannot exceed 30 cm
      - ◆ Typically 100 follicular units/cm<sup>2</sup> in donor strip
      - ◆ Leaves linear scar in occipital scalp
      - ◆ Grafts divided from strip
    - Follicular unit extraction
      - ◆ Punch removal of follicular units using manual, motorized, or robotic tools
      - ◆ Each follicular unit typically consists of 2 to 3 hair shafts
      - ◆ Less visible scarring
      - ◆ Preferred in individuals with short hair, risk of hypertrophic/keloid scar, and in younger patients
  - **Posttransplant telogen effluvium** occurs 2 to 3 weeks later (self-resolves)
  - **New hair growth 10 to 20 weeks postsurgery**, but overall effect apparent at 6 to 9 months
  - Selected SEs: lidocaine toxicity, ingrown hairs, hypoesthesia/numbness (usually resolves within a few weeks), cobblestoning, postoperative edema of forehead (resolves within 1 to 2 weeks generally), infection, and hypertrophic/keloidal scarring at donor site

## 9.8 CHEMICAL PEELS

See [Table 9-16](#).

Table 9-13. Cosmeceuticals and Antioxidants

Ingredients	Antioxidant Capacity	Decreases Inflammation	Skin Hydration	Reduces Pigment	Reduces Redness	Smooths Skin Texture	Fights Wrinkles	Improves Barrier Function	Wound Healing Benefits	Anti-Microbial Properties	Other Important Information/Benefits
Aloe Vera	X	X	X						X	X	Uses: Acute frostbite, Lichen Planus, Wound Healing, Psoriasis, Venous leg ulcers
Anica	X	X							X		Uses: <b>Reduces bruising and purpura</b> Chemical Classification: sesquiterpene lactones
Bromelain		X								X	Uses: <b>Reduce bruising and purpura</b> , can potentiate antibiotics Source: proteolytic enzymes derived from stem of <b>pineapples</b>
Ceramides								X			Uses: Atopic Dermatitis
Chamomile		X	X								Uses: Can be used to enhance the color of blonde hair Classification: Emollient
Kojic Acid	X			X					X		Uses: <b>Melasma</b>
Licochalcone (licorice extract)					X					X	Uses: Rosacea
Niacinamide	X	X	X	X	X			X			Uses: <b>Acne, Rosacea</b>
Resveratrol	X	X		X	X		X		X		Uses: Keloid scars, antiproliferative effects
Soy	X	X					X				Uses: Often combined with sodium sulfacetamide. Used for Acne, Seborrheic Dermatitis, Rosacea, Scabies, Tinea Versicolor
Urea			X			X				X	Active ingredient: Phytoestrogens Uses: Xerosis, Psoriasis, Atopic Dermatitis, KP, Keratodermas, Ichthyosis Classification: Humectant
Vitamin B5			X								Classification: Humectant, Emollient
Vitamin C	X	X	X	X	X	X	X	X			–
Vitamin E	X		X					X			–
Vitamin K				X							Use: <b>↓bruising/purpura</b>
Zinc	X	X							X	X	Uses: Photoprotective, Acne, Seborrheic Dermatitis

**Table 9-14.** Basic Criteria for Assessment of Candidates for Hair Transplantation

Criteria	More Favorable	Less Favorable
Age	>25 years old is preferable	15–25 years of age
Caliber of hair shaft	Large caliber (> 70 microns)	Small caliber hair
Donor hair characteristics	>80 follicular units/cm <sup>2</sup>	<40 follicular units/cm <sup>2</sup>
Degree of baldness	Baldness primarily affecting frontal scalp	
Hair color	“Salt and pepper,” red, or blonde hair	Black hair

*Adapted from Bologna JL, Jorizzo JL, Schaffer JV (2012) Dermatology.*

**Table 9-15.** Comparison of Elliptical Donor Harvesting Versus Follicular Unit Extraction

	Elliptical Donor Harvesting	Follicular Unit Extraction
Transection of hair follicles	Minimal	Variable
Time required to perform harvest	10–20 minutes	30–90 minutes
Need to create grafts	Yes	No
Visible scar with a short hair cut	Yes	No

*Adapted from Bologna JL, Jorizzo JL, Schaffer JV (2012) Dermatology.*

**Table 9-16.** Chemical Peel Agents

Chemical Peel	Depth of Peel	Use	Neutralization Required?	Frost Level(*)	High Yield Facts
Salicylic Acid	Superficial (papillary dermis)	<b>Acne</b> , photoaging	No	Minimal	<ul style="list-style-type: none"> <li>• <b>β-hydroxy</b> acid</li> <li>• Keratolytic and comedolytic → most commonly used for <b>acne</b></li> <li>• Pregnancy C</li> <li>• Immediate white frosting</li> <li>• May cause <b>tinnitus</b></li> <li>• <b>Safe in Fitzpatrick V &amp; VI skin</b></li> </ul>
Glycolic Acid	Superficial (papillary dermis)	Fine Wrinkles, dyspigmentation, melisma	Yes ( <b>sodium bicarbonate</b> )	<b>None</b>	<ul style="list-style-type: none"> <li>• <b>α-hydroxy</b> acid</li> <li>• Pregnancy B</li> <li>• No frosting, no peeling</li> </ul>
TCA 10–25%	Superficial (papillary dermis)	Fine wrinkles, dyspigmentation, melisma, acne	No	Minimal to none	<ul style="list-style-type: none"> <li>• Frosting generally only occurs when concentrations exceed 25%</li> </ul>
Jessner's Peel ( <i>salicylic acid, lactic acid, and resorcinol ethanol</i> )	Superficial (papillary dermis)	Fine Wrinkles, melasma	No	<b>None</b>	<ul style="list-style-type: none"> <li>• Pregnancy C</li> <li>• Know the components comprising Jessner's (Mnemonic: “<b>JESNR is LESR</b>” = Lactate, Ethanol, Salicylic acid, Resorcinol)</li> <li>• Salicylic acid component may cause <b>tinnitus</b></li> <li>• <b>Resorcinol</b> may cause <b>syncope &amp; hypothyroidism</b></li> <li>• Combined Jessner's-TCA (35%) peel has been shown to be as effective as Efficacy in treating AKs</li> </ul>
TCA 35%–50%	Medium (upper reticular dermis)	Fine to Medium Wrinkles, actinic keratoses, dyspigmentation, seborrheic keratoses	No	I–II	<ul style="list-style-type: none"> <li>• May be used as field treatment for severe photodamage with numerous AKs</li> <li>• Frosting occurs within 2 minutes (self-resolves in 15–20 minutes)</li> <li>• <b>Post-peel erythema</b> may last up to 1 month</li> </ul>
TCA >50%	Deep (mid-reticular dermis)	Fine to Deep Wrinkles, warts	No	III	<ul style="list-style-type: none"> <li>• Most common side effect is <b>depigmentation</b></li> <li>• <b>Scarring</b> is common → high concentration TCA peels (&gt;50%) are not generally recommended (Baker-Gordon phenol peels are preferred)</li> </ul>
Baker-Gordon Peel ( <i>Phenol, septisol, tap water, croton oil</i> )	Deep (mid-reticular dermis)	Fine to Deep Wrinkles	No (but use <b>mineral oil</b> rather than water to flush eyes if contact occurs)	III	<ul style="list-style-type: none"> <li>• Contraindications: Dark skin, history of cardiac arrhythmias, history of renal or liver disease</li> <li>• <b>Hypopigmentation</b> is common → contraindicated in dark-skinned patients</li> <li>• <b>Scarring</b> and/or <b>milium</b> formation may occur</li> <li>• <b>Cardiac monitoring</b> required during, and 1hr postop, due to <b>arrhythmia risk</b> → ↓risk by only treating over 60–90 minutes with a 15 minute interval between each cosmetic unit (decreases systemic absorption)</li> <li>• ↑risk of <b>renal toxicity</b> if inadequately hydrated → <b>IV hydration</b> recommended to reduce risk</li> <li>• Post-peel erythema lasts ≥ 3 months</li> <li>• Boards Fodder: Efficacy is most strongly related to <b>Croton oil</b></li> </ul>

\*Frost Levels: I – Minimal frosting with minimal erythema; II – Significant frosting with moderate erythema; III – Enamel-like whitening with no erythema.  
 General points: HSV prophylaxis in those with history of HSV; superficial (epidermis to papillary dermis) vs. medium (papillary to upper reticular dermis) vs. deep (mid reticular dermis) peel



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# Cutaneous Manifestations of Internal Disease and Metastases

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- Many of the diseases discussed in this section involve more than one organ system; however, in the interest of conserving space, we have made an attempt to categorize the diseases with their predominant affected organ system
- Many of the following tables have been adapted from those in the *Dermatologic Manifestations in Patients with Systemic Disease* chapter in Bologna JL, et al. *Dermatology Essentials*. Elsevier, 2014; please refer to this excellent chapter for further reading
- KEY: AD, autosomal dominant; AR, autosomal recessive

## 10.1 CARDIOVASCULAR/ CARDIOPULMONARY

### Behçet's disease

#### Cutaneous findings

- Orogenital aphthous ulcers, pustular vasculitis, and pathergy

#### Associations/comments

- A/w pericarditis, coronary arteritis, valve disease, CNS vasculitis, and ocular disease (e.g. vasculitis, uveitis

[panuveitis > posterior uveitis > anterior uveitis], vitritis, retinitis)

### Birt-Hogg-Dubé syndrome

#### Cutaneous findings

- Fibrofolliculomas, trichodiscomas, perifollicular fibromas, and acrochordons (Fig. 10-1); lesions most commonly affect head/neck; lesions tend to present in 30s–40s

#### Genetics

- Folliculin (FLCN) gene mutation (involved in mTOR pathway)

#### Associations/comments

- Fibrofolliculoma, trichodiscoma, perifollicular fibroma and acrochordons are identical lesions just viewed in different histologic planes
- Important associated findings:
  - Pulmonary cysts (most common; up to 90%) lead to spontaneous pneumothorax (30%)
  - Multiple renal carcinomas (15%, most commonly chromophobe renal carcinoma and oncocytoma)



**Figure 10-1.** (A) Trichodiscomas and (B) fibrofolliculomas and acrochordons in a patient with Birt-Hogg-Dubé. (With permission López V, Jordá E, Monteagudo C. Birt-Hogg-Dubé Syndrome: An Update. *Actas Dermo-Sifiliográficas* (English Edition) 2012;103(3):198–206)

- Medullary thyroid carcinoma
- +/- colon cancer (inconclusive association)

### Cardio-facio-cutaneous syndrome (CFC)

#### Cutaneous findings

- Coarse facies (long and broad), generalized ichthyosis-like scaling, keratosis pilaris, CALMs, nevi, and sparse curly hair

#### Genetics

- AD; one of the RASopathies; mutations in **BRAF** (most common) and other MAPK pathway genes

#### Associations/comments

- A/w mental retardation, **pulmonic stenosis**, atrial septal defect, **hypertrophic cardiomyopathy**, and short stature
- All **RASopathies** (CFC, NF1, Noonan, Costello syndromes, and LEOPARD) affect RAS/MAPK pathway and have similar clinical presentations → often need genetic tests to distinguish

### Carney complex (LAMB and NAME syndromes)

#### Cutaneous findings

- LAMB = Lentigines, Atrial (and cutaneous) Myxomas, Blue nevi (classically **epithelioid blue nevi**)
- NAME = Nevi, Atrial (and cutaneous) Myxomas, Ephelides

#### Genetics

- AD, mutations in **PRKAR1A** gene (encodes subunit of Protein Kinase A)

#### Associations/comments

- A/w variety of **endocrine neoplasms**;
  - most commonly affected = **adrenal gland**; p/w primary pigmented nodular adrenocortical disease → **Cushing's**
  - Other endocrine abnormalities: pituitary adenomas and testicular cancer (Sertoli type)
- A/w **psammomatous melanotic schwannoma**

### Carvajal Syndrome

#### Cutaneous findings

- **Striate epidermolytic palmoplantar keratoderma**; **wooly scalp hair**

#### Genetics

- AR, **desmoplakin** mutations

#### Associations/comments

- A/w dilated **left ventricular cardiomyopathy**
- Mnemonic: "Carvajal = Linear/striate PPK + Left ventricular cardiomyopathy"

## Churg-Strauss syndrome (allergic granulomatous angiitis)

### Cutaneous findings

- Skin involvement in 60%; LCV, urticaria, livedo reticularis, subcutaneous nodules, PNGD (palisaded neutrophilic granulomatous dermatitis), and extravascular granulomas

### Associations/comments

- Most commonly a/w **allergic rhinitis**, **severe asthma**, **peripheral eosinophilia** of  $\geq 10\%$ , sinusitis, transient pulmonary infiltrates, and mononeuritis multiplex
- $\uparrow$ IgE levels
- Most common causes of mortality: myocarditis and coronary arteritis
- ANCAs detectable in 50%; **p-ANCA** (anti-MPO)  $\gg$  c-ANCA (PR-3)
- ANCAs less frequently positive compared with Wegener's (50% vs  $\sim 100\%$ )
- May be a/w **leukotriene inhibitors** (montelukast and zafirlukast)

## Costello syndrome

### Cutaneous findings

- **Lax skin** on hands and feet, **coarse facies**, low-set ears, deep palmoplantar creases, periorificial papillomas, acanthosis nigricans, and curly hair

### Genetics

- AD, one of the RASopathies; mutations in **HRAS** (85%)  $>$  **KRAS** (10%–15%)

### Associations/comments

- A/w mental and growth retardation, **pulmonic stenosis**, hypertrophic cardiomyopathy, and arrhythmias
- $\uparrow$ risk of rhabdomyosarcoma and transitional cell (bladder) CA
- All **RASopathies** (CFC, NF1, Noonan, Costello syndromes, and LEOPARD) have similar clinical presentations  $\rightarrow$  need genetic tests to distinguish

## Cutis laxa

### Cutaneous findings

- Loose, **pendulous skin** of face (esp. periorcular and cheeks  $\rightarrow$  "**bloodhound facies**"), neck, axillae, and thighs; skin lacks elastic recoil (vs EDS)

### Genetics

- Multiple forms:
  - AR: **most common** and most severe; **Fibulin-5** (FBLN5)

- AD: benign course; **Elastin (ELN)**  $>$  FBLN5
- XLR: ATP7A (copper transporter)

### Associations/comments

- **Occipital horn syndrome** is the current name for XLR cutis laxa, (which was also formerly called Ehlers-Danlos type IX); OHS a mild variant of **Menkes kinky hair syndrome**
- AR cutis laxa is most frequently a/w internal organ dysfunction and death:
  - Pulmonary: bronchiectasis, emphysema  $\rightarrow$  **right-sided heart failure**
  - Cardiac: **aortic dilation/rupture**; right-sided heart failure
  - GI: **diverticulae**

## Dermatomyositis

### Cutaneous findings

- Gottron's papules, heliotrope rash, **shawl sign**, **holster sign**, photodistributed poikiloderma, and psoriasiform dermatitis of scalp

### Associations/comments

- A/w ECG changes and pericarditis
- **Cardiac involvement** = poor prognostic sign; a/w **anti-SRP autoantibodies**
- **Pulmonary fibrosis** a/w **antisynthetase syndrome** (Jo-1, PL7, and PL-12; autoantibodies target tRNA synthetase)

## Ehlers-Danlos syndrome (classic form)

### Cutaneous findings

- Skin hyperelasticity, "cigarette paper" and "fish mouth" scars, ecchymoses, Gorlin sign, and molluscoid pseudotumors

### Genetics

See [Table 4-13](#). Ehlers-Danlos Syndrome Classification in Pediatric Dermatology chapter

### Associations/comments

- A/w aortic root dilation, **mitral and tricuspid prolapse** or regurgitation
- Identical cardiac findings may also be seen in **hypermobility** type of EDS (traditionally, EDS type III)

## Ehlers-Danlos syndrome (vascular form; formerly type IV EDS)

### Cutaneous findings

- **Thin, translucent skin** w/ **visible veins** (most prominent on chest), diffuse bruising



## Genetics

- AD; caused by mutations in **collagen III (COL3A1)**

## Associations/comments

- Most **dangerous form** of EDS because of the risk of death from rupture of internal organs (**arterial rupture** > GI tract [esp. sigmoid colon], uterus [particularly in pregnancy])
  - Arterial rupture sites: thorax/abdomen > head/neck > extremities
- Most important feature is **vascular fragility** → **arterial aneurysms, dissection, and rupture** (Mnemonic: “IV = vascular”)

## Endocarditis

## Cutaneous findings

- Purpura, **Janeway lesions** (not painful; palms and soles), **Osler’s nodes** (painful; “Osler’s = Oww!”; fingers and toes) nail-fold infarction

## Associations/comments

- A/w **cardiac vegetations** and valvular dysfunction

## Erythroderma

## Cutaneous findings

- Diffusely red skin, exfoliative dermatitis

## Associations/comments

- A/w **high-output cardiac failure**
- May be as a result of multiple dermatoses, CTCL, or drug eruptions

## Fabry disease

## Cutaneous findings

- **Angiokeratoma corporis diffusum** (angiokeratomas in “bathing suit distribution”), hypohidrosis, episodic pain in hands/feet (**acroparesthesia**), and **whorled corneal opacities** (cornea verticillata)

## Genetics

- XLR; GLA gene mutation → **α-galactosidase** deficiency

## Associations/comments

- Most serious complications: atherosclerotic disease of CV and CNS → **MI** and **stroke**; chronic proteinuria → **renal failure**
- α-galactosidase deficiency leads to ↑**globotriaosylceramide** deposits in tissues → end organ damage

- “**Maltese crosses**” (birefringent lipid globules) seen on polarization of urine sediment

## Hemochromatosis

## Cutaneous findings

- Generalized **bronze hyperpigmentation**

## Genetics

- **HFE gene** mutation

## Associations/comments

- A/w **CHF** (congestive heart failure), supraventricular arrhythmias, diabetes mellitus, and cirrhosis

## Hereditary hemorrhagic telangiectasia (pulmonary disease in type I > type II)

## Cutaneous findings

- Multiple macular/“**mat-like**” **telangiectasias** most commonly on **lips, oral mucosa, and extremities** (Fig. 10-2)

## Genetics

- AD, mutations in genes involved in **TGF-β** transduction pathway:
  - HHT1 = **endoglin (ENG)**
  - HHT2 = **Alk-1 (ACVRL1)**

## Associations/comments

- **Epistaxis** (often the initial symptom), AV malformations of **lungs** (HHT-1 most commonly), **liver** (HHT-2 most commonly) and CNS; recurrent upper GI hemorrhage
- \*Mnemonic: “**Alk-1 is a/w liver**” (think of Alkaline phosphatase, which is found in liver)



**Figure 10-2.** Patient with HHT and multiple telangiectasias on tongue and lip. (With permission Irani F, Kasmani R. Hereditary hemorrhagic telangiectasia: fatigue and dyspnea. Can Med Assoc J 2009;180(8):839–839)

## Homocystinuria

### Cutaneous findings

- **Livedo reticularis**, malar rash, tissue-paper scars, diffuse pigment dilution, **Marfanoid habitus**, and **ectopia lentis** (downward lens dislocation)

### Genetics

- AR; caused by a variety of mutations leading to ↑homocysteine levels in blood and urine; most common = **cystathionine β-synthase (CBS gene)**
  - Other gene mutations: **MTHFR**, **MTR**, **MTRR**, and **MMADHC**

### Associations/comments

- A/w atherosclerosis and vascular thrombosis (arterial + venous)
- A/w mental retardation and seizures

## Hyperlipoproteinemias

### Cutaneous findings

- Type I (familial LPL deficiency and hyperchylomicronemia): **eruptive xanthomas**
- Type II (familial hypercholesterolemia): **tendinous, tuberous**, tuboeruptive, **interdigital xanthomas** (pathognomonic), and plane xanthomas
- Type III (familial dysbetalipoproteinemia, “broad beta disease”): tendinous, tuberous, tuboeruptive xanthomas, and **plane xanthomas of palmar creases** (pathognomonic)
- Type IV (endogenous hypertriglyceridemia): **eruptive xanthomas**
- Type V: **eruptive xanthomas**

### Genetics

- Type I: **LPL deficiency** and ApoC-II deficiency
- Type II: **LDL receptor** defect and ApoB-100 defect
- Type III: **ApoE** abnormality (results in ↓hepatic clearance)
- Type IV: ↑VLDL as a result of diabetes, alcoholism, and/or obesity
- Type V: ↑chylomicrons and VLDL; as a result of **diabetes**

### Associations/comments

- Associated systemic findings:
  - Type I, type IV, and type V: **acute pancreatitis** (as a result of ↑TGs)
  - Type II and III: atherosclerosis → **MI and stroke**

## Kawasaki disease

### Cutaneous findings

- “**Strawberry tongue**,” cheilitis, polymorphous skin eruption (favors trunk), **acral erythema/edema**

(w/ subsequent desquamation), **conjunctival injection**, and anterior uveitis

### Associations/comments

- A/w **coronary artery aneurysms** (potentially fatal)
- **High fever lasting ≥5 days**, cervical lymphadenopathy, truncal rash, hand edema/desquamation, oral findings, and conjunctival injection are diagnostic features
- Rx: high dose **ASA** and **IVIG** are essential to prevent coronary disease

## LEOPARD syndrome

### Cutaneous findings

- **Lentigines** (upper half of body; appear in childhood), **CALMs**, ocular hypertelorism (widely spaced eyes), **low-set ears**

### Genetics

- AD; is one of the RASopathies; most common mutation is **PTPN11 gene** (90%)
  - Less common mutations in MAPK pathway (10%): **BRAF** and **RAF1**

### Associations/comments

- ECG abnormalities, Pulmonary stenosis, Abnormalities of genitalia (cryptorchidism #1, hypospadias), Retardation of growth, and Deafness
- Hard to clinically distinguish from other RASopathies (CFC, NF1, Noonan, and Costello syndromes)

## Lymphomatoid granulomatosis

### Cutaneous findings

- Dermal or SQ nodules +/- ulceration on trunk and extremities

### Associations/comments

- **Frequently fatal** (60% 5-year mortality), EBV-induced **angiodestructive B-cell lymphoma**
- Classically p/w **pulmonary + skin** involvement

## Marfan syndrome

### Cutaneous findings

- **Striae**, long and narrow face, **ectopia lentis** (upward lens dislocation), myopia, arachnodactyly, and pectus excavatum

### Genetics

- AD; gene mutation in **Fibrillin-1**

### Associations/comments

- A/w mitral valve prolapse and regurgitation, aortic root dilation, and dissection of ascending aorta
- Rx: **β-blockers** and **ACE inhibitors** to prevent aortic root dilation

### Neonatal lupus erythematosus (NLE)

#### Cutaneous findings

- Nonscarring, nonatrophic SCLE-like **annular plaques** (most commonly **periocular**), and prominent **telangiectasias**

#### Associations/comments

- NLE a/w **congenital heart block** in up to 30% of pts (often irreversible; up to 30% mortality)
- Caused by transplacental passage of maternal **anti-Ro/SSA** antibodies (>anti-La/SSB > anti-U1RNP)
- Mothers who have one child w/ NLE have **25% recurrence rate** in subsequent pregnancies

### PHACES syndrome

#### Cutaneous findings

- Segmental infantile hemangioma (most commonly **frontotemporal**), typically on face and neck

#### Associations/comments

- A/w coarctation of the aorta, atrial septal defect, and ventricular septal defect
  - P: posterior fossa malformations
  - H: hemangiomas
  - A: arterial anomalies
  - C: cardiac defects and coarctation of the aorta
  - E: eye anomalies
  - S: sternal defects and supraumbilical raphe

### Naxos syndrome

#### Cutaneous findings

- **Diffuse** nonepidermolytic palmoplantar keratoderma, **wooly scalp hair**

#### Genetics

- AR, **plakoglobin** mutation

#### Associations/comments

- A/w arrhythmic **right ventricular** cardiomyopathy

### Neurofibromatosis Type 1 (NF-1)

#### Cutaneous findings

- **CALMs**, axillary freckles ("**Crowe's sign**"; seen in 30%; may involve neck and other intertriginous sites), multiple neurofibromas, and **Lisch nodules** (iris)

#### Genetics

- AD; mutation in **NF1** gene (neurofibromin)

#### Associations/comments

- A/w HTN (essential HTN and 2° to pheochromocytoma)

### Primary systemic amyloidosis (AL amyloidosis)

#### Cutaneous findings

- **Petechiae/pinch purpura** most common skin finding; may also see shiny, translucent **waxy papulonodules** or plaques, **alopecia**, and **macroglossia**

#### Associations/comments

- A/w **restrictive cardiomyopathy**, conduction abnormalities, and proteinuria
- As a result of deposition of immunoglobulin **light chains (AL)** in skin and internal tissues; deposits stain **pink-red w/ Congo red** (**apple-green birefringence** on polarized light)
- Primary systemic amyloidosis a/w skin findings in 30%; **secondary systemic amyloidosis does NOT produce clinical skin changes**

### Progeria (Hutchinson-Gilford progeria)

#### Cutaneous findings

- **Sclerodermoid changes**, **characteristic facies** (prominent eyes, thin **beaked nose**, protruding ears, and micrognathia), mottled hyperpigmentation, **↓SQ fat**, and **alopecia**

#### Genetics

- AD; mutations in **lamin A** (**LMNA** gene; component of nuclear lamina)

#### Associations/comments

- Most important association: premature death as a result of **atherosclerosis**, **MI**, or **stroke**

## Psoriasis

### Associations/comments

- ↑risk of **cardiovascular, cerebrovascular, and peripheral arterial diseases**; ↑risk of metabolic syndrome

## Relapsing polychondritis

### Cutaneous findings

- Intense erythema of cartilaginous portion of ears (**sparing earlobes**) + inflammation of other cartilaginous tissues (nose and trachea)

### Associations/comments

- A/w tracheal and nasal collapse
- A/w aortic insufficiency and dissecting aortic aneurysm

## Rheumatic fever

### Cutaneous findings

- Erythema marginatum, subcutaneous nodules, polyarthritis, chorea, and fever

### Associations/comments

- Acute phase: pericarditis
- Chronic: **mitral and aortic valve disease**

## Sarcoidosis

### Cutaneous findings

- Red-brown papules, nodules, and plaques w/ "apple jelly" color on diascopy; may arise in preexisting scars; **lupus pernio** (strongly a/w lung disease), EN (a/w acute bilateral hilar adenopathy and arthritis of ankles = Lofgren syndrome)

### Associations/comments

- Pulmonary: pulmonary artery HTN and **interstitial lung disease**
- Cardiac: **pericarditis** and conduction defects; cardiac involvement a/w poor prognosis

## Systemic lupus erythematosus

### Cutaneous findings

- Transient malar erythema; photosensitivity +/- DLE and SCLÉ lesions
- If antiphospholipid antibodies present: necrotizing livedo reticularis, widespread cutaneous necrosis, and leg ulcers

### Associations/comments

- A/w **Libman-Sacks endocarditis** (nonbacterial), pericarditis, and coronary artery disease

## Wegener's granulomatosis (granulomatosis with polyangiitis, GPA)

### Cutaneous findings

- Skin involvement in 50%; LCV, necrotizing cutaneous granulomas, pyoderma gangrenosum-like lesions ("malignant pyoderma"), **friable ulcerative gingivae** (**strawberry gingivae**), mucosal ulcerations, and "saddle nose"

### Associations/comments

- Severe (>90% mortality if untreated) multisystem **necrotizing vasculitis**
- Most common systemic manifestations: **respiratory tract** (**chronic sinusitis** is most common presenting symptom of GPA); **renal** (segmental crescentic necrotizing glomerulonephritis)
- **c-ANCA** (anti-Proteinase-3) autoantibodies in ~100% of pts by ELISA and IIF; detectable ANCA more common in GPA than in Churg-Strauss (50%)

## Yellow nail syndrome

### Cutaneous findings

- Thick, **slow-growing**, highly curved, and yellow or **yellow-green nails** w/ onycholysis; absent cuticles and lunulae

### Associations/comments

- **Classic triad**: yellow nails, lymphedema, and pulmonary disease (bronchiectasis and pleural effusions)

## 10.2 ENDOCRINE

### DIABETES

## Bullous diabeticorum

### Cutaneous findings

- Tense, noninflammatory, painless bullae on upper and/or lower extremities (**Fig. 10-3**)

### Associations/comments

- Usually heals in 2 to 4 weeks
- M > F
- Treatment with supportive care

## Benign acanthosis nigricans

### Cutaneous findings

- Velvety, brown, digitate plaques on neck and in axillary and inguinal folds





**Figure 10-3.** Bullous diabeticorum on the lower extremity. (From Bologna JL, et al. *Dermatology Essentials*. Elsevier, 2014)

### Associations/comments

- Slow onset, usually manifests earlier in life
- Can indicate insulin resistance and/or diabetes
- More common in darkly pigmented individuals
- Treatment includes improvement of insulin resistance, topical retinoids, ammonium lactate, and calcipotriene

### Granuloma annulare

#### Cutaneous findings

- Often affects trunks and extensor limbs, or may be generalized and eruptive; p/w nonscaly, flesh-colored, pink, violaceous, or reddish brown papules that can be grouped in an arcuate or annular pattern

### Associations/comments

- Usually asymptomatic and spontaneously resolves over months to years
- DDx: NLD (favors lower legs), cutaneous sarcoidosis, lichen planus, and rheumatoid nodules
- Rx: observation, topical steroids, intralesional steroids, cryotherapy, and phototherapy
- May also be a/w hyperlipidemia

### Carotenemia

#### Cutaneous findings

- Diffuse orange-yellow discoloration

### Associations/comments

- Secondary to increase in serum carotene level

### Neuropathic ulcers

#### Cutaneous findings

- Ulcerations at pressure sites, commonly on sole of foot; painless

### Associations/comments

- As a result of sensory neuropathy commonly seen in diabetes

### Scleredema diabeticorum (adulorum of Buschke)

#### Cutaneous findings

- Erythematous or skin-colored induration of upper back/neck

### Associations/comments

- As a result of glycosaminoglycan deposition
- Histology: **square biopsy** sign, **pauci-cellular** dermis (vs ↑cellularity in scleromyxedema), and **widely spaced collagen bundles separated by mucin** (best seen w/ colloidal iron)
- May also be associated with *Streptococcus* infections and IgG-kappa monoclonal gammopathy

### Acral erythema

#### Cutaneous findings

- Erysipelas-like erythema of the hands and/or feet

### Associations/comments

- May be secondary to small vessel occlusive disease with compensatory hyperemia

### Diabetic dermopathy

#### Cutaneous findings

- Small, oval, red-brown, atrophic macules and patches that are usually on the lower limbs

### Associations/comments

- As a result of minor trauma and/or decreased skin perfusion from microangiopathy
- Early recognition can help detect early presence of renal and retinal microangiopathy

### Necrobiosis lipoidica diabeticorum (NLD)

#### Cutaneous findings

- **Atrophic yellow-orange patches** w/ red borders and **telangiectasias** +/- central ulceration, often on pretibial skin (Fig. 10-4); lesions may ulcerate and heal with **atrophic scars**

### Associations/comments

- A/w diabetic **nephropathy**, **retinopathy**, and **smoking**
- 30% of NLD pts have diabetes, but only 0.3% of diabetics have NLD
- F > M



**Figure 10-4.** NLD. (From Jones S, Hunter H. Skin manifestations of systemic disease. *Medicine* 2009;37(6):277–281)



**Figure 10-5.** Pretibial myxedema on the lower extremities. (From Brinster NK, et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011)

- Rx: topical or IL-steroids, fibrinolytics, pentoxifylline, and surgical treatments

## Multiple endocrine neoplasia (MEN)

### Cutaneous findings

- Type I (Wermer's) – **pituitary** gland adenomas, **parathyroid** tumors, and **pancreatic** tumors; tuberous sclerosis-like skin changes (collagenomas, facial angiofibromas, leukodermic macules, and CALMs, lipomas)
- Type IIa (Sipple syndrome) – **parathyroid** adenomas, **medullary thyroid** carcinoma, **pheochromocytoma** notalgia paresthetica, and macular/lichen amyloidosis
- Type IIb/III (multiple mucosal neuroma syndrome) – **mucosal neuromas**, **medullary thyroid** carcinoma, **pheochromocytoma**, GI ganglioneuromatosis, marfanoid habitus, and thickened lips

### Genetics

- AD
- Type I: **MEN1** (encodes menin, a tumor suppressor)
- Types IIa and IIb/III: **RET** (encodes a tyrosine receptor kinase)

### Associations/comments

- Most important mucocutaneous changes:
- MEN 1 = **TS-like** changes
- MEN 2a = **amyloid**
- MEN 2b = mucosal **neuromas**; **marfanoid** features

## Infections more common in diabetes

- Erythrasma
- Furuncles/carbuncles
- Candidiasis: angular cheilitis, median rhomboid glossitis, chronic paronychia, erosion interdigitale blastomycetica, genital infections, and intertrigo
- Other bacterial and fungal infections

## THYROID DISEASE

### Graves' disease

#### Cutaneous findings

- Velvety, smooth, or moist skin
- Localized or generalized hyperpigmentation
- Fine hair; mild but diffuse alopecia
- Koilonychia, onycholysis, and clubbing from **thyroid acropachy**

#### Pretibial myxedema

- **Indurated** red-brown **pretibial** plaques (>posterior-external forearms >> other sites) (Fig. 10-5)

#### Associations/comments

- Affects 3–5% of pts with Graves' disease
- Often occurs after surgical treatment of Graves' disease
- A/w exophthalmos, thyroid acropachy, clubbing, and trachyonychia

## Thyroid dermopathy

- Symmetric, nonpitting, yellow to red-brown, waxy papules, nodules, and plaques on upper/lower extremities

### Associations/comments

- Rx: topical and IL-steroids
- A/w hyperthyroidism

## Hypothyroidism

### Cutaneous findings

- Coarse, dry, scaly, cold, boggy, and edematous skin
- **Generalized** myxedema
- Dull, **brittle**, and **coarse hair**; diffuse alopecia
- **Madarosis** (loss of eyebrows/eyelashes), hypohidrosis, onycholysis, and striated/brittle/slow-growing nails
- Cutaneous pallor or **yellowing of skin** secondary to carotenemia
- Thickened skin with enlargement of the lips and tongue

## Thyroid cancer

### Cutaneous findings

- **Papillary** thyroid carcinoma is most common type to present as a skin metastasis

### Associations/comments

- Thyroid cancer is a/w multiple syndromes:
  - Medullary thyroid carcinoma: MEN IIA, MEN IIB, and Birt-Hogg-Dubé
  - Follicular thyroid carcinoma: Cowden syndrome

## OTHER DISEASES

### Addison's disease

### Cutaneous findings

- **Diffuse hyperpigmentation** (accentuated in sun-exposed areas) secondary to ACTH secretion; fibrosis and calcification of cartilage; loss of ambisexual hair in postpubertal women

### Associations/comments

- As a result of adrenal insufficiency

### Cushing's syndrome

### Cutaneous findings

- Thin atrophic skin, easy bruising and poor wound healing, violaceous striae, buffalo hump, moon facies, steroid-induced acne, and hypertrichosis

## 10.3 GASTROENTEROLOGY

### Bannayan-Riley-Ruvalcaba syndrome

### Cutaneous findings

- Macrocephaly, **lipomas**, and **penile lentigines**

### Genetics

- AD, mutation in **PTEN gene** (encodes protein phosphatase); affects mTOR pathway

### Associations/comments

- Mild phenotypic variant of Cowden syndrome (much lower risk of visceral malignancy)
- A/w intestinal hamartomatous polyposis

### Blue rubber bleb nevus syndrome

### Cutaneous findings

- Multiple soft blue-purple subcutaneous "blebs" (**venous malformations**)

### Genetics

- Sporadic (>AD)

### Associations/comments

- Most important and common internal manifestation = GI venous malformations (blue blebs) → **GI hemorrhage** (potentially fatal)
- **Skin lesions precede** GI involvement (birth vs early adulthood, respectively) → early recognition of skin changes is important!

### Bowel-associated dermatosis-arthritis syndrome (BADAS, bowel-bypass syndrome)

### Cutaneous findings

- Erythematous macules and patches with overlying papulovesicles and pustules on proximal extremities and trunk

### Associations/comments

- P/w fevers, chills, malaise, arthritis, and skin findings
- As a result of **bowel bacterial overgrowth** leading to complement activation and deposition of antibody complexes in skin/synovium
- 20% are a/w jejunoileal **bypass surgery** for obesity
- May be a/w **IBD**
- Rx: **antibiotics** (TCN, quinolones, metronidazole, and macrolides) and topical steroids; consider surgical revision of bowel bypass if severe

## Cirrhosis

### Cutaneous findings

- Spider angiomas, palmar erythema, gynecomastia, Terry's nails (liver failure), Muehrcke's nails (hypoalbuminemia), pruritus, and jaundice

## Cowden syndrome (PTEN hamartoma syndrome)

### Cutaneous findings

- Facial trichilemmomas, oral papillomas (tongue, gingivae most commonly), palmoplantar keratoses, multiple lipomas, sclerotic fibromas (pathognomonic), and penile lentigines

### Genetics

- AD, mutation in **PTEN** (encodes protein phosphatase); affects mTOR pathway

### Associations/comments

- A/w hamartomatous polyps in GI tract, fibrocystic breast disease
- Lifetime risk of cancer: **Breast** (85%; often bilateral) > **Thyroid** (35%; follicular most common) > **Endometrial**
- \*Mnemonic: "BET on cancer with Cowden's"
- Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease) is just a part of Cowden's syndrome; is a hamartoma that leads to cerebellar ataxia, macrocephaly, and ↑intracranial pressure
- PTEN Hamartoma syndrome (PTHS)**: umbrella term encompassing Cowden's syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and Proteus-like syndrome; all diseases have overlapping features

## Cronkhite-Canada syndrome

### Cutaneous findings

- Lentiginous hypermelanosis, alopecia, and nail thinning

### Associations/comments

- A/w nonhereditary adenomatous polyposis, diarrhea/malabsorption (leading to weight loss), edema, and abdominal pain
- No ↑risk of cancer

## Degos disease (malignant atrophic papulosis)

### Cutaneous findings

- Eruption of multiple papules with porcelain-white center and erythematous rim; most commonly affects upper extremities and trunk

## Associations/comments

- Is an **occlusive vasculopathy** of small arteries w/ **poor prognosis** (exception: skin-limited form has good prognosis)
- A/w **GI perforation** (most common and most severe complication; occurs in half of cases; high mortality) > CNS disease

## Dermatitis herpetiformis (Dühring's disease)

### Cutaneous findings

- Itchy papulovesicles and erosions on extensor extremities, scalp, and buttocks

### Genetics

- Associated with: **HLA-DQ2 > HLA-DQ8** >> other cited haplotypes (HLA-A1, HLA-B8, HLA-DR3)

### Associations/comments

Very strong association with gluten-sensitive enteropathy/ celiac disease

- Poor adherence to gluten-free diet → ↑risk GI lymphoma

## Gardner syndrome (phenotypic variant of familial adenomatous polyposis syndrome)

### Cutaneous findings

- Multiple epidermoid cysts** (often hybrid cysts w/ focal pilomatrical differentiation), **multiple pilomatricomas**, **multiple lipomas**, desmoid tumors (15%), fibromas, jaw osteomas, and odontogenic cysts

### Genetics

- AD mutation in **APC gene** (normally functions to downregulate β-catenin)

### Associations/comments

- A/w many neoplasms: **colorectal** (~100%) carcinoma
- A/w congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Syndromes a/w multiple pilomatricomas**: Gardner, Rubenstein-Taybi, myotonic dystrophy
- Syndromes a/w multiple lipomas**: Gardner, Bannayan-Riley-Ruvalcaba, and MEN-I

## Hemochromatosis

### Cutaneous findings

- Generalized bronzing and hyperpigmentation

### Genetics

- Mutation in **HFE gene** (C282Y most common)



### Associations/comments

- A/w excess iron stores, cirrhosis, cardiac dysfunction, and diabetes mellitus
- Rx: phlebotomy (first line) and chelation (second line)

### Hepatitis B and C

#### Cutaneous findings

- Most important Hep B associated diseases:
  - Gianotti-Crosti ( $B \gg C$ )
  - Classic PAN ( $B > C$ )
  - EN ( $B > C$ )
- Most important Hep C associated diseases:
  - Necrolytic acral erythema (C)
  - Erosive oral LP (C)
  - Cryoglobulinemia types 2 and 3 ( $C \gg B$ )
  - PCT ( $C > B$ )
  - Cutaneous PAN ( $C > B$ )
  - Sarcoidosis a/w IFN or ribavirin ( $C > B$ )

### Associations/comments

- Other associated diseases (Hep B = C): EM, CSSV, pruritus, urticarial vasculitis, and urticaria

### Inflammatory bowel disease (IBD)

#### Cutaneous findings

- Cutaneous findings vary depending on disease association

### Associations/comments

- A/w erythema nodosum, urticarial vasculitis, small vessel vasculitis, PAN, bowel-associated dermatosis-arthritis syndrome, **pyoderma gangrenosum**, neutrophilic dermatosis, pyostomatitis vegetans, aphthous ulcers, granulomatous infiltrates, fissures, fistulas, and epidermolysis bullosa acquisita

### Primary biliary cirrhosis

#### Cutaneous findings

- Pruritus, jaundice, diffuse hyperpigmentation, and xanthomas

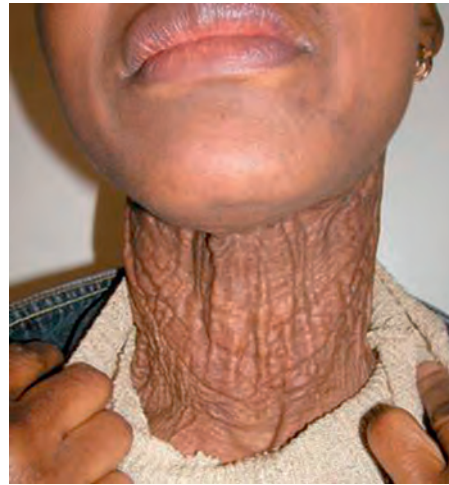
### Associations/comments

- Autoimmune disease strongly a/w **antimitochondrial antibodies** (>90%)
- $F \gg M$  (9:1)
- Osteoporosis is common complication
- Rx: ursodiol, colchicine, methotrexate, and transplant

### Peutz-Jeghers syndrome

#### Cutaneous findings

- Mucosal (> cutaneous) melanotic macules



**Figure 10-6.** Lax skin and redundant folds on the anterior neck of a patient with PXE. (With permission Akram H, Sewell M, Cheng L. Pseudoxanthoma elasticum. Brit J Oral Maxillo Surg 2008;46(3):237–238)

### Genetics

- AD, mutation of serine/threonine protein kinase (STK11)

### Associations/comments

- Benign hamartomatous polyps of the digestive tract (minimal to no malignant potential)
- Most important associated malignancies: **breast** (~50%) > **GI** (~40%) and **pancreatic** (~35%–40%)

### Pseudoxanthoma elasticum (PXE)

#### Cutaneous findings

- Yellow papules in **intertriginous** areas, along with redundant, lax skin (Fig. 10-6)

### Genetics

- AR **ABCC6** gene mutation (ABC transporter/ATPase involved in multidrug resistance)

### Associations/comments

- A/w **GI hemorrhage**, **angioid streaks** (small breaks in Bruch's membrane), hypertension, **premature atherosclerosis**, MI, uterine hemorrhage, and vascular calcification
- Angioid streaks a/w: PXE, Paget's bone disease, sickle cell anemia, and lead poisoning

### Pyoderma gangrenosum (PG)

#### Cutaneous findings

- Violaceous nodule or hemorrhagic pustule that progresses to an ulcer with **undermined purpuric borders** (Fig. 10-7); ulcer base may be purulent and hemorrhagic with necrotic eschar; ulcers heal with



**Figure 10-7.** Pyoderma gangrenosum on the lower extremity of a patient with ulcerative colitis. (From Brinster NK, et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011)

cribriform scarring; most commonly affects lower extremities

### Associations/comments

- A/w IBD (ulcerative colitis > Crohn's disease), rheumatoid arthritis, and myeloid blood dyscrasias
- Can show pathergy

### Pyodermatitis/pyostomatitis vegetans

#### Cutaneous findings

- Pustules and ulcerations on lips, buccal mucosa (Fig. 10-8), and skin folds
- A/w pyoderma gangrenosum of the skin

### Associations/comments

- Almost always a/w IBD (ulcerative colitis > Crohn's disease)
- Rx: Treat underlying IBD; may use topical steroids or tacrolimus for local control

### Muir-Torre syndrome (phenotypic variant of Lynch syndrome)

#### Cutaneous findings

- Multiple sebaceous neoplasms: sebaceous adenoma, sebaceoma, and sebaceous carcinomas
- Multiple keratoacanthomas (often w/ sebaceous differentiation)



**Figure 10-8.** Patient with pyostomatitis vegetans exhibiting erythematous oral mucosa with overlying yellow pustules. (From Islam N, Bhattacharyya I, Cohen D. Common Oral Manifestations of Systemic Disease. *Otolaryng Clin N Amer* 2011;44(1):161–182)

### Genetics

- AD, mutations in mismatch repair genes → microsatellite instability; most common mutations: MSH2 (90%) > MSH6, MLH1, and PMS-2

### Associations/comments

- Cancer associations: colon (most common, 50%) > GU (second most common) > gastric, ovarian, endometrial cancers, and lymphoma
- Extrafacial sebaceous neoplasms are very strongly a/w Muir-Torre (more so than facial lesions)
- KAs w/ sebaceous differentiation strongly a/w Muir-Torre

### Scleroderma (systemic sclerosis)

#### Cutaneous findings

- Early bilateral edema of hands progressing to acrosclerosis, dermal sclerosis (most commonly arms and head/neck); also see Raynaud phenomenon w/ digital infarction, ventral pterygium, facial telangiectasias (esp. CREST variant), and “salt and pepper” dyspigmentation; dermoscopy of nail folds show dilated capillary loops w/ surrounding avascular areas

### Associations/comments

- Dermal sclerosis as a result of TGF- $\beta$  (and endothelin-1, PDGF, IL-4, and connective tissue growth factor)
- Most commonly a/w esophageal dysmotility and pulmonary fibrosis (up to 60%)
- Anti-topoisomerase I (Scl-70): a/w diffuse SSc and pulmonary fibrosis
- Anticentromere antibodies: a/w CREST syndrome (ISSc), and  $\downarrow$ pulmonary, cardiac, and renal involvement
- Anti-PM/Scl antibodies: a/w polymyositis-scleroderma overlap syndrome



**Figure 10-9.** Perifollicular purpura and follicular hyperkeratosis seen in scurvy. (From Fitzpatrick JE, Morelli JG. *Dermatology Secrets Plus*, 4th Ed. Elsevier, 2011)

## Scurvy (vitamin C deficiency)

### Cutaneous findings

- Perifollicular purpura, “corkscrew hairs,” follicular hyperkeratosis, gingivitis, conjunctival hemorrhage, anemia (from GI blood loss), and difficulty walking (Fig. 10-9)

### Associations/comments

- A/w fad diets, malnutrition, and alcoholism
- Vitamin C (ascorbic acid) is **cofactor** for lysyl hydroxylase and prolyl hydroxylase (required for collagen hydroxylation and subsequent cross-linking) → **defective collagen cross-linking** → bone deformities, vascular fragility, poor wound healing, and aforementioned skin findings

## Spider angioma

### Cutaneous findings

- Red macule or papule with vascular extensions, typically planar

### Associations/comments

- Occurs secondary to **hyperestrinism**
- Develops in at least 75% of those with **cirrhosis**; also can occur with **pregnancy** and **oral contraceptive use**

## Wilson disease (hepatolenticular degeneration)

### Cutaneous findings

- Kayser-Fleischer rings, blue lunulae, and pretibial hyperpigmentation

### Genetics

- AR mutation in ATP7B

### Associations/comments

- Defects in copper metabolism → deposition in liver and subsequent liver failure
- Neuropsychiatric symptoms common
- Ceruloplasmin levels low
- Kayser-Fleischer rings as a result of copper deposition in **Descemet’s membrane** (cornea)
- Rx: penicillamine, trientine, or liver transplantation

## 10.4 NEUROLOGY

- There are several neurologic conditions with cutaneous manifestations and they are discussed in greater detail throughout several other chapters of this book
- See Pediatric Dermatology section for review of neurofibromatosis, basal cell nevus syndrome, ataxia-telangiectasia syndrome, xeroderma pigmentosum, Sjögren-Larsson syndrome, Refsum disease, Cockayne, incontinentia pigmenti, KID syndrome, Vohwinkel syndrome, Bjornstad syndrome, PIBIDS, and Menkes disease

## 10.5 RENAL

### Birt-Hogg-Dubé syndrome (see Cardiopulmonary section of this chapter)

- **Multiple renal carcinomas** (15%, most commonly chromophobe renal carcinoma and oncocytoma)

### Calciophylaxis

### Cutaneous findings

- P/w painful “stellate” or **retiform** purpuric plaques on **lower legs** → indurated, necrotic, ulcerative plaques

### Associations/comments

- As a result of small to medium vessel **calcification + thrombosis**
- Most commonly occurs in setting of end stage renal disease (a/w ↑**calcium-phosphate product**)  
Other causes: diabetes mellitus and hyperparathyroidism
- A/w secondary infections and sepsis; **high mortality**
- Rx: treat underlying renal failure, partial parathyroidectomy, debride necrotic tissue, sodium thiosulfate, and treat underlying infections; Mayo Clinic has reported success w/ fibrinolytic therapies

### End stage renal disease (ESRD)

### Cutaneous findings

- Pale color, **yellowing of skin** secondary to deposition of carotenoids and urochrome, photo-distributed

hyperpigmentation, ecchymoses, xerosis, and Lindsay's (half and half) nails

### Associations/comments

- Pruritus, calciphylaxis, metastatic calcification, nephrogenic fibrosing dermopathy/NSF (a/w gadolinium exposure), perforating diseases, uremic frost, pseudoporphyria, and porphyria cutanea tarda

### Henoch-Schönlein purpura (HSP)

#### Cutaneous findings

- LCV (favors legs and buttocks)

### Associations/comments

- May be a/w IgA glomerulonephritis
- Most common in prepubescent children; majority of pts have preceding URTI/pharyngitis; group A *Streptococcus* is most common associated infection
- P/w abdominal pain, scrotal pain/edema, arthritis, and transient renal insufficiency (may have chronic renal insufficiency in up to 10%–20%, but only 2% develop ESRD)

### Nail-patella syndrome (iliac horn disease and HOOD syndrome = hereditary oncho-osteodysplasia)

#### Cutaneous findings

- Hypoplasia of nails (fingernails > toenails; thumb most severely affected), triangular lunulae

### Genetics

- AD LMX1B gene mutation (regulates collagen synthesis)

### Associations/comments

- A/w focal segmental glomerulosclerosis (seen in 40%, fatal in 10%; important to treat early to prevent renal failure), absence/hypoplasia of patella (90%), iliac horns (pathognomonic exostoses of iliac bone of pelvis, seen in 80%; asymptomatic)
- Classic eye finding: Lester iris (~50%; hyperpigmentation of pupillary margin of iris)

### Nephrogenic systemic fibrosis (NSF); prior name: nephrogenic fibrosing dermopathy (NFD)

#### Cutaneous findings

- Woody, indurated plaques most commonly on legs (> trunk) with "peau d'orange" appearance; face spared and yellow papules on palms

### Associations/comments

- All pts have history of exposure to gadolinium MRI contrast dye (highest risk w/ Omniscan, Magnevist, and Optimark) in setting of renal insufficiency (chronic > acute)
- Important eye finding: yellow scleral plaques

### Polyarteritis nodosa (PAN)

#### Cutaneous findings

- Dermal/SQ nodules and livedo reticularis

### Associations/comments

- Classic associations: renal artery aneurysms and HTN

### Reed's syndrome (familial cutaneous leiomyomas)

#### Cutaneous findings

- Multiple cutaneous pilar leiomyomas and uterine leiomyomas

### Genetics

- AD, fumarate hydratase gene mutation
- Fumarate hydratase is an enzyme involved in citric acid/Krebs cycle of cellular respiration

### Associations/comments

- ↑risk of renal cell carcinoma (15% lifetime risk) and renal cysts

### Tuberous sclerosis

#### Cutaneous findings

- Facial angiofibromas in butterfly distribution (adenoma sebaceum), periungual and subungual angiofibromas (Koenen's tumors), ash leaf macules, shagreen patch (back/neck most common), CALMs, and ocular lesions (coloboma and phakoma)

### Genetics

- AD; caused by mutations in TSC1 (hamartin) and TSC2 (tuberin)

### Associations/comments

- A/w renal angiomyolipomas, CNS tumors (giant cell astrocytoma, cortical tubers, subependymal nodules), mental retardation, seizures, and cardiac rhabdomyomas



## 10.6 PARANEOPLASTIC SYNDROMES

### Acquired angioedema (AAE)

#### Cutaneous findings

- Painless, nonpitting, pruritic edema of the skin; no associated urticarial

#### Associations/comments

- Caused by ↓C1-INH activity (common to all forms of HAE and AAE)
- Both types AAE (AAE1 and AAE2) have ↓C1q (distinguishes from HAE) and ↓C2/C4
  - AAE type 1 a/w lymphoproliferative disease
  - AAE type 2 a/w autoimmune disease

### Acquired ichthyosis

#### Cutaneous findings

- Adherent **polygonal** scale/keratosis on **lower extremities** (favors extensors); spares flexural creases

#### Associations/comments

- Most commonly a/w **Hodgkin and non-Hodgkin lymphoma**
- Other associations: sarcoidosis, lupus, thyroid dysfunction, drugs, lymphoma, breast and lung cancer
- Usually diagnosed after malignancy and course follows that of underlying malignancy

### Acrokeratosis paraneoplastica (Bazex syndrome)

#### Cutaneous findings

- Initially p/w **symmetric** erythematous to **violaceous** psoriasiform plaques on **nasal bridge, helices, distal extremities**, +/- palmoplantar keratoderma; eruption gradually extends proximally to knees, legs, arms, and scalp (Fig. 10-10)
- Other clinical findings include xanthonychia, subungual hyperkeratosis, onycholysis, and **horizontal and longitudinal nail ridging** (seen in 75%)

#### Associations/comments

- Most commonly a/w cancer of **upper aerodigestive tract** (oral cavity, pharynx, larynx, esophagus)
- Can clinically resemble psoriasis (involvement of helices and nose is a clue to Bazex)
- M > F; average age = 40
- Skin findings precede the diagnosis by 2–6 months



**Figure 10-10.** Nail dystrophy and erythematous to violaceous plaques in a patient with Bazex syndrome. (Rigel, et al. Cancer of the Skin. Elsevier, 2011)

### Alopecia neoplastica

#### Cutaneous findings

- **Localized scarring alopecia** as a result of dermal infiltration by metastatic carcinoma

#### Associations/comments

- A/w metastatic breast cancer

### Antiepileptin cicatricial pemphigoid

#### Cutaneous findings

- Severe, scarring **mucocutaneous** bullous disease affecting mouth, eyes, genitalia, and skin

#### Associations/comments

- A/w variety of **adenocarcinomas** (GI and lung > gynecologic and GU > others)

### Carcinoid syndrome

#### Cutaneous findings

- Head, neck, and upper trunk **flushing** and erythema; **pellagra-like dermatitis**, diarrhea, dyspnea, **wheezing**, and bronchospasm; sclerodermoid changes in advanced disease

#### Associations/comments

- ↑5-HIAA levels can be found in urine
- **Metastasis to liver** is typically required for **midgut tumors** to produce carcinoid syndrome
- **Bronchial and gastric** carcinoid tumors may cause flushing in **absence of liver metastases**
- Although the **appendix is the most common** location for primary carcinoid tumors, it very rarely metastasizes to liver → rarely causes carcinoid syndrome

## Carcinoma en cuirasse/ carcinoma erysipeloides

### Cutaneous findings

- Carcinoma en cuirasse: indurated skin w/ orange peel-like (*peau d'orange*) appearance
- Carcinoma erysipeloides: well-demarcated, raised red plaque
- Both typically present on the chest wall, but can also involve axilla and upper extremities

### Associations/comments

- As a result of **metastatic breast carcinoma** infiltration into lymphatic vessels

## Cryoglobulinemia type I

### Cutaneous findings

- Retiform purpura and necrosis on **cool acral sites**; acral cyanosis and livedo reticularis

### Associations/comments

- As a result of monoclonal gammopathy (typically in the form of a plasma cell dyscrasia such as multiple myeloma, B-cell lymphoma or Waldenström macroglobulinemia)
- Histology: vessels plugged with pink proteinaceous material (immunoglobulins)

## Cutaneous metastases

### Cutaneous findings

- Erythematous and violaceous papules and nodules

### Associations/comments

- Cutaneous metastases occur most commonly from breast cancer in women and lung cancer in men
- Other cancers with a high cutaneous metastatic potential include: colon, melanoma, and larynx/oral cavity/nasal sinus
- Metastases from renal carcinoma appear as highly vascular papules and nodules on the head/neck

## Dermatomyositis

### Cutaneous findings

- Classic DM changes

### Associations/comments

- Most commonly a/w **ovarian cancer**
- Other associated malignancies: lung, colorectal, pancreatic, and non-Hodgkin lymphoma



**Figure 10-11.** Erythematous, serpiginous, and polycyclic patches with scale and desquamation in a patient with erythema gyratum repens. (With permission De La Torre-Lugo E, Sánchez J. Erythema gyratum repens. J Amer Acad Dermatol 2011;64(5):e89–e90)

## Ectopic ACTH syndrome

### Cutaneous findings

- Generalized hyperpigmentation

### Associations/comments

- Secondary to tumor production of ACTH (often **small cell carcinoma of the lung**)
- May show features of Cushing's syndrome

## Erythema gyratum repens (EGR)

### Cutaneous findings

- Widespread **serpiginous, polycyclic**, and pruriginous erythema with desquamating edges that produce concentric figures ("woodgrain" pattern) (Fig. 10-11)
- Spares hands and feet

### Associations/comments

- **Lung cancer** is most commonly associated malignancy (> esophageal and breast)
- Usually **precedes** detection of primary malignancy and resolves w/ treatment of underlying malignancy
- Average age = 60s; M > F (2 : 1)
- Plaques expand rapidly (~1 cm/day)

## Erythroderma

### Cutaneous findings

- Widespread erythema of total body w/ overlying scale; usually spares palms and soles

### Associations/comments

- May have alopecia, nail dystrophy, and ectropion
- Underlying **leukemias** and **lymphomas**



**Figure 10-12.** Extramammary Paget disease of the left inguinal crease and scrotum. (With permission Virich G, Gudi V, Canal A. Extramammary Paget's disease – occupational exposure to used engine oil and a new skin grafting technique. *J Plas Recon Aesth Surg* 2008;61(12):1528–1529)

## Extramammary Paget disease

### Cutaneous findings

- Red and white macerated/eroded plaques (“**strawberries and cream**”) located around anal verge and below dentate line (Fig. 10-12); most common sites are **vulva** (women) and **perianal** regions (men)

### Associations/comments

- **Primary EMPD (>75%)**: primary cutaneous adenocarcinoma; likely derived from **Toker cells** or cutaneous adnexal glandular epithelium (sweat glands); immunophenotype: **CK7<sup>+</sup>, GCFDP-15<sup>+</sup>, and CK20<sup>-</sup>**
- **Secondary EMPD (20%)**: may be as a result of direct extension or epidermotropic metastases of underlying GI/GU (> prostate, ovarian, and endometrial) adenocarcinoma; immunophenotype: **CK7<sup>+/−</sup>, GCFDP-15<sup>−</sup>, and CK20<sup>+</sup>**
- **High rate of recurrence**, even w/Mohs (because it is difficult to see individual Paget cells on frozen H&E sections); Mohs with CK7 immunostaining has improved cure rates (>95%); may try CO<sub>2</sub> laser ablation, radiotherapy, imiquimod, or 5-FU
- Five times ↑risk of internal malignancy w/ **perianal** EMPD vs vulvar and penoscrotal

## Familial atypical mole and multiple melanoma syndrome (FAMM syndrome)

### Cutaneous findings

- NIH consensus criteria:
  - Numerous (>50) melanocytic nevi, some of which are clinically dysplastic
  - Some nevi are histologically atypical
  - Family history of melanoma in one or more first-degree relatives



**Figure 10-13.** Increased lanugo hair on the nose and face of a man with underlying metastatic prostate cancer. (With permission Wyatt J, Anderson H, Greer K, et al. Acquired hypertrichosis lanuginosa as a presenting sign of metastatic prostate cancer with rapid resolution after treatment. *J Amer Acad Dermatol* 2007;56(2):S45–S47)

### Associations/comments

- AD; **CDKN2A** gene mutation (encodes two separate tumor suppressor proteins: **p16** and **p14/ARF**)
- **p16 inhibits CDK4**
- **p14/ARF inhibits MDM2** (normally degrades p53) → in normal state p14 indirectly increases p53 expression
- ↑risk of **pancreatic cancer**

## Howell-Evans syndrome (tylosis with oesophageal carcinoma, TOC)

### Cutaneous findings

- **Diffuse waxy keratoderma** of high pressure areas on plantar surface (i.e. heel, ball of foot) oral leukokeratosis

### Associations/comments

- AD, mutation of “**TOC gene**” on chromosome 17q25 (gene renamed **RHBDF2**)
- A/w esophageal carcinoma

## Hypertrichosis lanuginosa acquisita (‘malignant down’)

### Cutaneous findings

- Sudden onset of long, thin, soft, **lanugo-like hair** initially on the face and ears, which can spread in craniocaudal manner (Fig. 10-13)



### Associations/comments

- A/w **lung, colorectal, and breast cancer**; anorexia nervosa
- F > M (3:1); average age 40–70 years
- Tumor treatment usually leads to regression of hair growth

### Juvenile xanthogranuloma + neurofibromatosis type 1

#### Associations/comments

- Triple association w/ juvenile xanthogranuloma, neurofibromatosis type 1, and juvenile myelomonocytic leukemia

### Sign of Leser-Trélat

#### Cutaneous findings

- Sudden increase in the size and number of seborrheic keratoses

### Associations/comments

- Most commonly a/w underlying **gastric adenocarcinoma** (> colon, breast, others)
- A/w pruritus and inflammation; may improve with treatment of underlying malignancy
- May be a/w **acanthosis nigricans** and **tripe palms**

### Malignant acanthosis nigricans

#### Cutaneous findings

- Sudden onset with extensive and severe lesions; p/w symmetric hyperpigmented velvety plaques typically in intertriginous areas

### Associations/comments

- Typically a/w **GI cancer** (esp. stomach)
- Can occur simultaneously, before, or after cancer diagnosis and can have associated weight loss
- Improves with treatment of underlying malignancy
- 25% of patients also have **tripe palms** (tripe palms in absence of AN is more commonly a/w **lung cancer**)

### Multicentric reticulohistiocytosis

#### Cutaneous findings

- Multiple red to red-brown, nontender papules and nodules primarily on **dorsal hands** and **nail folds** with a “coral-beaded” appearance; face (esp. ears and perinasal) is second most common site

### Associations/comments

- Up to 50% have **arthritis mutilans**
- 25%–33% have **underlying malignancy** (no specific internal malignancy favored); skin eruption usually precedes diagnosis of internal malignancy



**Figure 10-14.** Erythematous, scaly plaques on lower abdomen of patient with necrolytic migratory erythema. (With permission Michels G, Nierhoff D, Steffen H. Necrolytic Migratory Erythema Due to Glucagonoma. Clin Gastroenterol Hepatol 2010;8(8):A18)

### Necrolytic migratory erythema (NME)

#### Cutaneous findings

- Arcuate and polycyclic, erosive, erythematous patches +/- vesicles/bullae often on **genital region, buttocks/anal region**, lower extremities, and intertriginous areas (Fig. 10-14)

### Associations/comments

- **Glucagonoma** syndrome consists of NME, glucose intolerance, weight loss, glossitis, and glucagon-secreting carcinoma
- A/w **pancreatic islet cell carcinoma** ( $\alpha$ -2 glucagon)

### Necrobiotic xanthogranuloma (NXG)

#### Cutaneous findings

- Indurated yellow plaques w/ frequent ulceration and necrosis (Fig. 10-15); most commonly **periorbital**

### Associations/comments

- A/w **paraproteinemia** (most often IgG- $\kappa$ ); occasionally a/w multiple myeloma and other lymphoproliferative malignancies

### Paget disease of the breast

#### Cutaneous findings

- Eczematous and psoriasiform plaques of the nipple

### Associations/comments

- Almost always a/w underlying **ductal breast CA**





**Figure 10-15.** Red-brown papules and plaques on the periorbital skin and cheek in a patient with NXG. (From Brinster NK, et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011)



**Figure 10-17.** Large, thin, yellow-orange plaque in a patient with monoclonal gammopathy. (From Bolognia JL et al. *Dermatology Essentials*. Elsevier, 2014)



**Figure 10-16.** Erosive and pustular hemorrhagic ulcers on the lips, tongue, and oropharynx of a patient with paraneoplastic pemphigus. (From Brinster NK, et al. *Dermatopathology: A Volume in the High Yield Pathology Series*. Elsevier, 2011)

## Paraneoplastic pemphigus

### Cutaneous findings

- Severe erosive disease of mucous membranes leading to painful oral stomatitis; polymorphous bullous skin eruption (individual lesions may resemble EM, LP, PV, or BP) (Fig. 10-16)

### Associations/comments

- 90% mortality; most common causes of death: underlying malignancy, bronchiolitis obliterans, and sepsis
- Most commonly a/w non-Hodgkin lymphoma or CLL
- Other associated malignancies: Castleman disease (most common association in children), thymoma, sarcoma
- No gender predominance; usually affects ages 45–70 years

## Pityriasis rotunda

### Cutaneous findings

- Multiple well-defined circular hyperpigmented and hypopigmented scaly patches, usually on the trunk/buttocks

### Associations/comments

- Most strongly a/w hepatocellular carcinoma
- Other associated conditions: tuberculosis, leprosy, and liver and lung disease; gastric and esophageal carcinoma

## Plane xanthoma

### Cutaneous findings

- Yellow patches and thin plaques (Fig. 10-17)
- Tends to affect trunk, periorbital skin, and body folds

### Associations/comments

- Often a/w paraproteinemia, multiple myeloma, and lymphoproliferative malignancies

## POEMS syndrome (Crow-Fukase syndrome)

### Cutaneous findings

- P: Polyneuropathy (distal → proximal motor and sensory)
- O: Organomegaly
- E: Endocrinopathy (number one is hypogonadism)
- M: M-protein (IgG and IgA light chains)
- S: Skin changes
  - Most common cutaneous findings: hyperpigmentation (90%), lower extremity edema >

hypertrichosis (80%), sclerodermoid changes > glomeruloid hemangiomas, cherry angiomas, and nail changes (leukonychia; clubbing) > acrocyanosis and Raynaud's

### Associations/comments

- Always a/w plasma cell dyscrasia: Waldenstrom macroglobulinemia, osteosclerotic myeloma, MGUS, and Castleman disease
- ↑↑VEGF levels
- Other associated findings include pulmonary effusions, ascites, peripheral edema, polycythemia, and thrombocytosis

### Primary systemic amyloidosis (AL amyloidosis)

#### Cutaneous findings

- Discussed in cardiopulmonary section

### Associations/comments

- Monoclonal gammopathy most commonly as a result of plasma cell dyscrasia >> multiple myeloma
- As a result of deposition of light chains (AL) in various tissues

### Schnitzler syndrome

#### Cutaneous findings

- Chronic urticaria in patient with fever, arthralgias, hepatosplenomegaly, and bone pain

### Associations/comments

- A/w IgM-κ paraproteinemia and lymphoplasmacytic malignancies

### Scleromyxedema

#### Cutaneous findings

- Widespread, firm, waxy papules often arranged in linear fashion; sclerodermoid skin changes; Leonine facies

### Associations/comments

- Invariably a/w paraproteinemia (most commonly IgGλ light chains); progresses to multiple myeloma in 10%

### Sister Mary Joseph nodule

#### Cutaneous findings

- Palpable nodule at umbilicus secondary to metastatic tumor



**Figure 10-18.** Tripe palms. (From Callen, et al. Dermatological Signs of Internal Disease 4th Ed. Elsevier, 2009)

### Associations/comments

- Typical source is malignancy of pelvis or abdomen including colon, ovarian, and pancreatic uterine and gastric cancer
- Has also been a/w breast cancer

### Sweet syndrome

#### Cutaneous findings

- "Juicy" red-violaceous papules/plaques that can have overlying pustules and pseudovesicles; favors head/neck, and upper extremities

### Associations/comments

- F > M (except in cases a/w underlying malignancy, where M = F)
- Also have fever, malaise, and leukocytosis
- A/w IBD, URI infection, malignancy (most common is AML), and polycythemia vera
- Rx: steroids, potassium iodide, clofazimine, and colchicine

### Tripe palms

#### Cutaneous findings

- Yellow, velvety, diffuse palmar hyperkeratosis with accentuated dermatoglyphic patterns (Fig. 10-18)

### Associations/comments

- Tripe palms + acanthosis nigricans → gastric cancer (most common)
- Tripe palms alone → lung cancer (most common)

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# 11

## Epidemiology, Statistics, Study Design, and Public Health Principles

*Anne L. Housholder*

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### 11.1 STATISTICAL DEFINITIONS

- Prevalence – total number of cases/total at risk population, most often stated as a percentage
- Incidence – number of new cases/total at risk population, most often stated as a percentage
  - Cumulative incidence is expressed over a given time frame
  - Incidence rate is the cumulative incidence divided by the time frame
- Precision – how consistently repeated are the assays of a test (reliability)
- Validity – how close an assay of a test comes to the truth (accuracy)

### 11.2 EPIDEMIOLOGIC PRINCIPLES

- Calculations using  $2 \times 2$  tables
- For the word problems you will encounter, a  $2 \times 2$  table can usually be constructed by identifying:
  - **Exposure** – the baseline characteristics of the study population
    - a. An intervention, e.g., drug administration, educational session
    - b. Assessment of a risk, e.g., smoking
    - c. For studies on diagnostic test accuracy – consider the test results as the exposure
  - **Outcome** – what happens during the study
    - a. A response to the intervention
    - b. Development of disease after exposure
    - c. For studies on diagnostic test accuracy – consider outcome, the true presence or absence of disease (see Table 11-1)
- Often one of these variables will not be given in the question stem and must be calculated from the given variables.  $a + b + c + d$  will always equal the total number of study subjects.
- For assessing diagnostic test accuracy:
  - Sensitivity – proportion of correctly identified positive results
    - $a / a + c$
    - High sensitivity means that if the test is negative, the disease is very likely to be absent because there are very few false negatives
  - Specificity – proportion of correctly identified negative results



**Table 11-1.** The True Presence or Absence of Disease

Exposure	Present	Absent
Exposed	a	b
Nonexposed	c	d

- $d/b + d$
- High specificity means that if the test is positive, the disease is very likely to be present because there are very few false positives
- Positive predictive value – likelihood that a person with a positive test result actually has the disease
  - $a/a + b$
  - More likely to be high for diseases with a high prevalence
- Negative predictive value – the likelihood that a person with a negative test result does not have the disease
  - $c/c + d$
  - More likely to be low for diseases with high prevalence
- The null hypothesis is the assumption that there is no difference between two groups being studied. After conducting the correct type of statistical testing, the null hypothesis may be rejected or accepted. A **type I error (false positive)** is the incorrect rejection of a true null hypothesis. The **type 1 error rate is called the alpha level**, for which the significance level may be set at a threshold, frequently 0.05 (equivalent to a false positive rate of 5%). If the p-value calculated from the data set is less than or equal to the alpha level then the result of the data is significant and the null hypothesis is rejected. A **type II error (false negative)** is the incorrect acceptance of a false null hypothesis. The **type II error rate is beta**, which is related to the power of the test ( $\text{power} = 1 - \text{beta}$ ). The larger the power of the test, the less likely the test is to produce a false positive. The power of the test is frequently increased by increasing the number of test subjects.

### 11.3 TYPES OF STUDIES AND THEIR LIMITATIONS

- Descriptive studies
  - Case reports, case series – offer the lowest level of evidence in favor of an intervention, but are very low cost and often provide sentinel observation (e.g., phocomelia in thalidomide use)
  - Cross-sectional survey – a type of **observational study** that provides information on the disease burden in a community that may be actionable (e.g., antibiotic-resistant organisms circulating in a community)
- Analytic studies
  - Case-control study
    - Type of **observational study** where two existing groups differing in already-known outcomes (e.g. disease vs. healthy) are retrospectively compared to see if the two groups have differences with regard to a suspected exposure.

- Example: Identify ESRD patients with nephrogenic systemic fibrosis (= known outcome) and a group of ESRD patients without NSF and see if there is a difference between the two groups with regard to exposure to a certain type of MRI contrast agent (= suspected exposure).
- Advantages: **cheaper and faster** to conduct than cohort studies or RCTs (since retrospective); especially useful for investigating **rare diseases** (since it takes a long time to accrue enough patients with rare diseases in prospective cohort studies or RCTs)
- An **odds ratio** can be calculated, which identifies the magnitude of the risk or protection afforded by the exposure
  - ◆ If the confidence interval is  $<1$ , protective; includes 1 if no discernible effect; if  $>1$  increased risk
- Cohort – a type of **observational study** where two populations are identified and segregated upon the basis of exposure to a variable of interest (exposed and unexposed groups) and then compared to see if there is a difference in terms of risk of developing an outcome of interest (e.g. disease)
  - Prospective – exposure status is identified before disease manifestation
    - ◆ Example: Identify two groups of people that are matched in every way (income, socioeconomic status, etc.) except that one group frequently uses tanning beds (= **exposure**; a.k.a. independent variable). Then monitor these groups over time to see if the two groups have different skin cancer rates (= **disease or outcome**; a.k.a. dependent variable).
    - ◆ **Relative risk** can be calculated
      - ➔ If the confidence interval is  $<1$  = protective; if it includes 1 = no discernible effect; if  $>1$  = increased risk
  - Retrospective – data on exposure is obtained from medical records, and records are followed to see outcomes
    - ◆ Example: retrieve all biopsies of nevi with severe cytologic atypia and look for new melanoma incidence documented in 10 years after diagnosis
    - ◆ **Relative risk** can be calculated
- Randomized control trial
  - Type of **interventional study** where study participants are randomly assigned to either a treatment group (group that receives the drug or intervention being investigated) or control group (do not receive the intervention being studied). The two groups are compared to see if there is a difference in outcomes (e.g. disease control, mortality rate, etc.)
  - **Gold-standard** for clinical trials, because the randomization minimizes selection bias and potentially confounding variables.
  - Example: Patients with delusions of parasitosis are randomly assigned to receive either a new study drug (intervention group), or a placebo (control group). They are then compared to see if there

is a difference in outcomes (e.g., disease control, improved QOL, etc.)

- Meta-analysis
  - Meta-analyses attempt to pool the data from all well designed available studies to reach a conclusion.
  - A well conducted meta-analysis based on multiple high-quality RCTs is the best evidence for or against an intervention (i.e., preferable to a single randomized controlled trial)

## 11.4 TYPES OF BIAS

- Biases that affect one arm of a study and not the other may affect the study results; their effect will either be to make it more likely find an effect that is not true, or to make it less likely to find an effect that is true; bias that affects both arms of a study may affect the study's generalizability
- Selection bias – the bias toward enrolling patients that do not represent the entire population of patients or controls; in referral centers the selection bias may be toward more severe disease, called spectrum bias; in nonrandomized studies, physicians may preferentially enroll sicker patients in treatment arms
- Information bias
  - Misclassification – occurs when the gold standard test cannot accurately differentiate between affected and unaffected persons
  - Recall – affects case-control studies where patients with a disease may be more likely to recall an exposure even though both groups received the exposure equally
  - Lead time – in observational studies, when a patient with a disease found earlier in its natural course appears to have a longer survival (either with or without treatment) due only to the time they are known to have the disease, and not because of a difference in response to treatment or a naturally slower progressing disease
  - Observer bias – unconscious assumptions or preconceptions of researchers that affect study design and results
  - Loss to follow-up – affects cohort studies when more patients are lost to follow-up preferentially from one group

- Confounding
  - When a third, and untested, variable exists that provides a probable explanation of the perceived association between the tested outcome and the exposure
    - This variable must be associated with the exposure, with a risk factor, and be independent of the pathway from the exposure to the disease

## 11.5 MAINTENANCE OF CERTIFICATION FOR THE AMERICAN BOARD OF DERMATOLOGY (see Table 11-2)

## 11.6 BILLING

- Evaluation and management codes (E/M) (Table 11-3)
  - Consist of three components:
    - History (chief complaint, history of present illness, review of systems, past medical, and social and family history)
    - Examination
    - Medical decision making
  - New patient – defined as not having been seen by a provider of the same specialty in the same group in the last 3 years; all three components must be at or above the level of complexity for the billed E/M code
  - Return patient – two of three components must be at or above the level of complexity for the billed E/M code
- Modifiers – coding numbers added to denote additional service provided on day of service
  - 25 – significant, separately identifiable E/M service by the same provider on the same day of the procedure or other service
  - 50 – bilateral procedure (e.g. Unna boot application)
  - 58 – Staged or related procedure or service by the same physician during the postoperative period (e.g. slow Mohs procedure)
  - 59 – a distinct service (separate from service rendered for the #25 modifier) e.g., separate procedure on separate site, e.g., biopsy of new lesion at time of ED&C of previously biopsied lesion.

**Table 11-2.** Maintenance of Certification for the American Board of Dermatology

Yearly	3X Per 10 Years	2X Per 10 Years	Every 10 Years
25 AMA level 1 credits	100 self-assessment questions	Practice improvement activities	Maintenance of certification examination and patient safety module
License attestation			
Annual fee			

Table 11-3. Evaluation and Management (E/M) Coding Criteria					
	99201 (new) 99211 (est.)	99202 (new) 99212 (est.)	99203 (new) 99213 (est.)	99204 (new) 99214 (est.)	99205 (new) 99215 (est.)
<b>History</b>					
CC	none	required	required	required	required
HPI	none	1-3 elements	1-3 elements	4+ elements (3+ if chronic dx)	4+ elements (3+ if chronic dx)
ROS	none	none	pertinent	2-9	10+
PFSH	none	none	none	1 element	2 elements
<b>Examination</b>					
1997 guidelines	none	1-5 elements	6-11 elements	12 or more elements	comprehensive
1995 guidelines	none	System of complaint	2-4 systems	5-7 systems	8+ systems
<b>Medical Decision Making</b>					
	none	straightforward	low	moderate	complex
<b>Time</b>					
(1/2 spent counseling or coordinating care)	5 min	10 min	15 min	25 min	40 min
<i>Est. = established; min = minutes; for established, need only 2 of 3 (history, examination, medical decision making)</i>					

- 79 – new problem arising during the global period:
  - After a procedure, you will not be paid for managing complications that arise as a result of that procedure (e.g., bleeding, postoperative infection); if the patient returns for a separate problem, you must associate the problem or treatment with a 79 modifier
  - All destruction, excision, and linear repair codes – 10-day global period
  - All flap (tissue transfer or rearrangement) and graft codes – 90-day global period
- Special procedural definitions
  - Shave removal: sharp removal transversely through dermis, without extension into fat
  - Excision: requires a full thickness removal (through the dermis and into the fat)

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